



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(54) Title: TECHNIQUES AND INTERMEDIATES FOR PREPARING NON-PEPTIDE PEPTIDOMIMETICS</p> <p>(57) Abstract</p> <p>Compounds are provided which are crossreactive with peptides such as those bound by G-protein-linked receptors, together with preparative and therapeutic methods therefor. In certain embodiments, 4-deoxy, 6-alkylamino glucopyranosides are prepared by coupling a protected, 4-deoxy, 6-hydroxy glucopyranoside with a protected alkylamine and then removing the alkylamine protecting group.</p>		

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**TECHNIQUES AND INTERMEDIATES FOR PREPARING  
NON-PEPTIDE PEPTIDOMIMETICS**

**GOVERNMENT SUPPORT**

Certain of the inventors may have been supported by National Institute of Mental Health Grant 45533 and National Institutes of Health Grant GM-41821.

**5 RELATED APPLICATION**

This application is a continuation-in-part of U.S. application Serial No. 748,826 filed August 22, 1991, entitled "Non-Peptide Peptidomimetics."

**FIELD OF THE INVENTION**

10 This invention relates to synthetic compounds which mimic or inhibit the biological and/or chemical activity of peptides, including compounds which are bound by G-protein-linked receptors. This invention also relates to techniques and intermediates useful in preparing in these synthetic  
15 compounds.

**BACKGROUND OF THE INVENTION:**

Peptides are implicated in a wide variety of biochemical processes in humans and other mammals. For  
20 example, it is known that a number of hormones and neurotransmitters are controlled by receptor-mediated stimulation of one or more of a family of guanine nucleotide-binding regulatory proteins, known as G-proteins. G-proteins activate or inhibit different effector enzymes, modulating the

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levels of intracellular secondary messengers. At least 50 sub-types of G-protein-linked receptors have been identified, among them the  $\alpha$ -adrenergic,  $\beta$ -adrenergic, muscarinic, cholinergic, dopamine, histamine, adenosine, serotonin, prostaglandin, leukotriene, thromboxane, prostacyclin, PAF, cAMP, enkephalin, endorphin, cholecystokinin, bombesin, substance K, substance P, neuromedin, bradykinin, FMLP, C5a, C3a, vasopressin, oxytocin, angiotensin, VIP, parathyroid hormone, calcitonin, neurotensin, TRH, somatostatin, rhodopsin, epinephrine, norepinephrine, acetylcholine, S-hydroxytryptamine, thyrotropin, thyrotropin releasing hormone, follicle stimulating, lutropin, choriogonadotropin, thrombin, retinal, and olfactory receptors. Nine or more G-proteins and at least seven effector systems have also been described. All of the G-protein-linked receptors analyzed to date contain from one to three potential sites of asparagine-linked glycosylation.

The transmembrane signaling pathway used by G-protein-linked receptors represents one of the major mechanism of signal transduction in cellular systems. It is known, for example, that substance P acts as a vasodilator, a depressant, stimulates salivation, and produces increased capillary permeability. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. In addition to substance P (neurokinin-1, NK-1), the known mammalian tachykinins include neurokinin A (NK-2) and neurokinin B (NK-2). The tachykinins have been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease.

Substance P is known to produce both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal and plays a role in sensory transmission and pain perception. Substance P also is believed to be involved in the inflammatory response in

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diseases such as rheumatoid arthritis and osteoarthritis. Other disease areas where the tachykinins are believed to be involved include allergic conditions, immunoregulation, bronchospasm, reflex or neuronal control of the viscera, and  
5 Alzheimer's disease and Downs Syndrome.

To date, there have been limited therapeutic applications involving peptides, due in considerable part to lack of oral bioavailability and to proteolytic degradation. Typically, for example, peptides are rapidly degraded in vivo  
10 by exo- and endopeptidases, resulting in generally very short biological half-lives. Another deficiency of peptides as potential therapeutic agents is their lack of bioavailability via oral administration. Degradation of the peptides by proteolytic enzymes in the gastrointestinal tract is likely  
15 an important contributing factor. The problem is, however, more complicated, because it has been recognized that even small, cyclic peptides which are not subject to rapid metabolic inactivation nevertheless exhibit poor oral bioavailability. This likely is due to poor transport across  
20 the intestinal membrane and rapid clearance from the blood by hepatic extraction with subsequent excretion into the intestine. These observations suggest that multiple amide bonds may interfere with oral bioavailability.

The design of peptide mimics which are resistant to  
25 degradation by proteolytic enzymes has become of increasing interest to peptide chemists, both for hormone agonist/antagonist and for enzyme inhibitor design. A primary goal has been to reduce the susceptibility of mimics to cleavage and inactivation by peptidases. In one approach,  
30 such as disclosed by Sherman and Spatola, *J. Am. Chem. Soc.*, 112, 1990, 433, one or more amide bonds have been replaced in an essentially isosteric manner by a variety of chemical functional groups. This stepwise approach has met with some success in that active analogs have been obtained. In some  
35 instances, these analogs have been shown to possess longer biological half-lives than their naturally-occurring counterparts. Nevertheless, this approach has limitations.

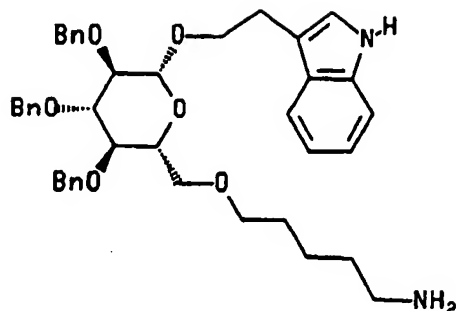
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Successful replacement of more than one amide bond has been rare. Consequently, the resulting analogs have remained susceptible to enzymatic inactivation elsewhere in the molecule. Moreover, this approach does not permit  
5 generalizations between chemically unrelated peptides concerning permissible amide mimic substitutions.

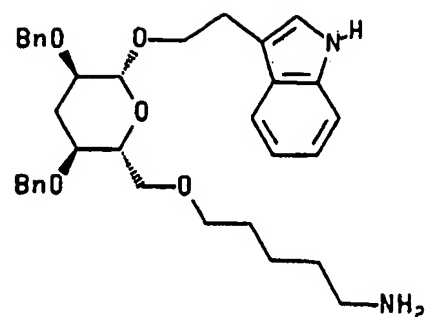
In another approach, a variety of uncoded or modified amino acids such as D-amino acids and N-methyl amino acids have been used to modify mammalian peptides.  
10 Alternatively, a presumed bioactive conformation has been stabilized by a covalent modification, such as cyclization or by incorporation of  $\gamma$ -lactam or other types of bridges. See, e.g., Veber and Hirschmann, et al., *Proc. Natl. Acad. Sci. USA*, 1978 75 2636 and Thorsett, et al., *Biochem. Biophys. Res.*  
15 *Comm.*, 1983 111 166. The primary purpose of such manipulations has not been to avoid metabolism or to enhance oral bioavailability but rather to constrain a bioactive conformation to enhance potency or to induce greater specificity for a receptor subtype.

20 Another approach, disclosed by Rich, D.H. in *Protease Inhibitors*, Barrett and Selveson, eds., Elsevier (1986), has been to design peptide mimics through the application of the transition state analog concept in enzyme inhibitor design. For example, it is known that the secondary  
25 alcohol of statine mimics the tetrahedral transition state of the scissile amide bond of the pepsin substrate. Again, increased potency rather than decreased susceptibility to peptidases or increased bioavailability was the principal objective. Moreover, the transition state analog concept has  
30 no apparent relevance to hormone agonist/antagonist design.

Nicolaou and Hirschmann, et al., *Design and synthesis of a peptidomimetic employing  $\beta$ -D-glucose for scaffolding*, in *Peptides*, Rivier and Marshall, eds., ESCOM (1990), disclosed non-peptide somatostatin mimics having  
35 structures (1) and (2), wherein Bn is benzyl.



(1)



(2)

These mimics were bound by somatostatin receptors of AtT-20 cells with  $IC_{50}$  of about  $9.5 \times 10^{-6}$  M and about  $1 \times 10^{-6}$  M, respectively, compared with an  $IC_{50}$  of about 9.3 nM ( $9.3 \times 10^{-9}$  M) for somatostatin itself. Significantly, the mimics failed to bind other G-protein-linked receptors at clinically acceptable concentrations. For example, while it was found that the  $\beta$ -adrenergic receptor, which is also found in AtT-20 cells, bound mimic (1), it required a five fold higher concentration to do so than was required for the somatostatin receptor. The goal of the authors was to increase the specificity of the mimics for the somatostatin receptor, not to develop compounds which would be bound by G-protein-linked receptors. Indeed, the authors suggested increasing the potency of the compounds as a means for enhancing this specificity.

Accordingly, there remains a long-felt need for metabolically stable chemical compounds which exhibit both good bioavailability and the capacity to be bound by a variety of G-protein-linked receptors.

#### OBJECTS OF THE INVENTION

It is one object of the present invention to provide compositions of matter which mimic or inhibit the biological and/or chemical activity of peptides.

It is another object to provide compositions which are chemically more stable than naturally-occurring peptides, particularly under conditions such as found in the human body.

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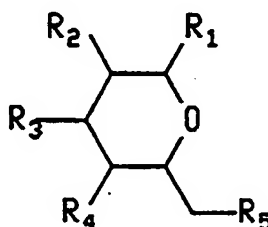
It is a further object to provide compositions which function as hormone agonists or hormone antagonists.

It is a further object to provide compositions which effectively are bound by G-protein-linked receptors, especially the substance P receptor.

It is still a further object to provide prophylactic, diagnostic, and therapeutic uses for peptide analogs.

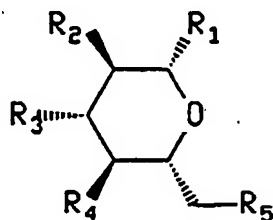
#### SUMMARY OF THE INVENTION

These and other objects are accomplished by the present invention, which provides compounds, known as peptide analogs, which contain no peptide bonds yet which mimic or inhibit the chemical and/or biological activity of peptides. In general, the peptide analogs have structure (3):

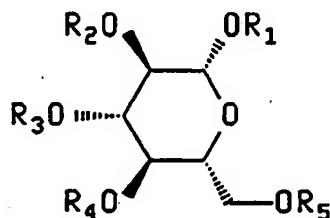


(3)

wherein at least one of  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , or  $R_5$  comprises a chemical functional group which causes the compounds to be crossreactive with the peptide of interest. In preferred embodiments, peptide analogs invention have structure (4) and, more preferably, structure (5):



(4)



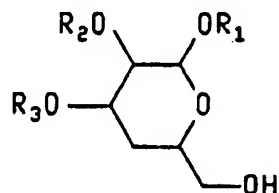
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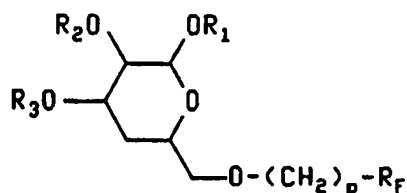
Compounds having these structures have been found to effectively be bound by a number of G-protein-linked receptors. Indeed, it has even been discovered in accordance with the present invention that the compounds having  
 5 structures (1) and (2) are bound by G-protein-linked receptors other than the SRIF receptor.

The present invention also provides processes and chemical intermediates useful in preparing the peptide analogs. In certain embodiments, 4-deoxy peptide analogs are  
 10 prepared by processes that include providing a first compound having structure (14):



(14)

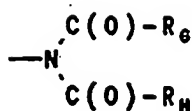
wherein  $R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups. The first compound is contacted  
 15 with a second compound having structure  $L-(CH_2)_p-R_F$  ( $L$  = leaving group) in the presence of a suitable base to form a protected amine having structure (15):



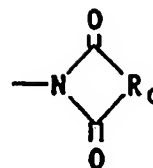
(15)

wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as above,  $R_F$  has structure (16) or  
 20 (17),  $R_G$  and  $R_H$  are, independently, alkyl or alkenyl having from one to about 10 carbon atoms, and  $p$  is an integer from 0 to about 10.

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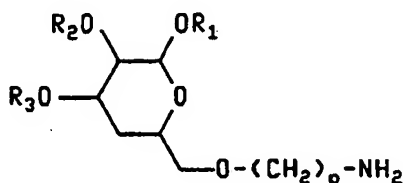


(16)



(17)

Protected amine (15) is then contacted with a base that does not remove the hydroxyl protecting groups to form primary amine (18).



(18)

It has been discovered that these and other peptide analogs can mediate the chemical and/or biological effects of hormone agonists/antagonists or other peptides. The peptide analogs of the invention are believed to possess beneficial properties such as increased half-life, lack of immunogenicity, and the ability to cross the blood-brain barrier; they are believed to be useful for the development of pharmaceutical, therapeutic, and diagnostic techniques. Accordingly, the invention also provides methods for producing a prophylactic or therapeutic response in a mammal by administering to the mammal a pharmaceutically effective amount of one or more peptide analogs of the invention. In accordance with preferred embodiments, the present invention provides methods for producing such responses by modulating the activity of at least one mammalian G-protein-linked receptor by administering an effective amount of one or more peptide analogs of the invention.

#### DETAILED DESCRIPTION OF THE INVENTION

It has been found in accordance with the present invention that non-peptide compounds which mimic or inhibit

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the chemical and/or biological activity of a variety of peptides can be produced by appending to certain core species such as the tetrahydropyranyl ring of structure (3) chemical functional groups which cause the compounds to be at least partially crossreactive with the peptide. As will be recognized, compounds which mimic or inhibit peptides are to varying degrees crossreactive therewith. In accordance with the present invention, crossreactive moieties are those which compete with one another in binding G-protein-linked receptors through one of the many chemical reaction phenomena known in the art such as, for example, complexation, crystallization, or ionic, hydrogen, or covalent bonding. Thus, it is intended that the term "crossreactive" include both agonism and antagonism. Those skilled in the art recognize that a substance which competes with a peptide ligand in cell receptor binding is described as an agonist if the response of the cell is the same as or mimics the action of the peptide ligand. A substance that competes with the peptide ligand in receptor binding is referred to as antagonist if it blocks or inhibits the action of the cell to the action of the ligand.

There exist a wide variety of useful analytical techniques for elucidating the precise structure of a peptide. These techniques include amino acid sequencing, x-ray crystallography, mass spectroscopy, nuclear magnetic resonance spectroscopy, computer-assisted molecular modeling, peptide mapping, and combinations thereof. Structural analysis of a peptide generally provides a large body of data which in preferred embodiments comprises the amino acid sequence of the peptide as well as the three-dimensional positioning of its atomic components. It is believed that only certain of these components, which are known both individually and collectively as chemical functionality, participate in any given reaction phenomena. It will be appreciated that the participation of a chemical functional group in peptide reactivity is manifested by the linkage or coordination of the functional group with at least a portion of a complementary reactive moiety such as a hormone receptor. Such linkage or binding

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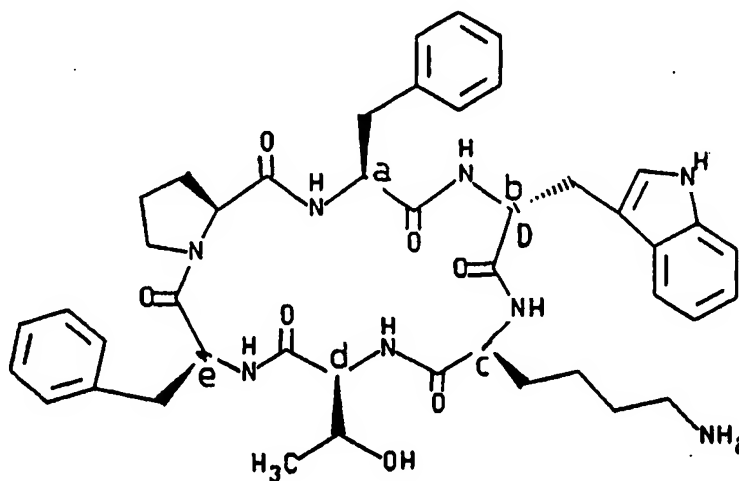
may be effected through a covalent, ionic, or hydrogen bond or some weaker atomic coordination effect such as complexation or crystallization.

In accordance with the present invention, peptide  
5 chemical functionality which participates in binding is identified by one of the many techniques known in the art. For example, such identification can be effected through a stepwise process wherein one or more peptide analogs are prepared. For example, peptide analogs having structure (3)  
10 can be prepared by substitution at certain of the positions  $R_1$ - $R_5$  with chemical functionalities which are crossreactive with functionalities found in the peptide. The activity of the analog in a binding assay is then compared with that of the peptide. The degree to which the binding of the analog  
15 corresponds with that of the peptide indicates the degree to which the substituents participate in the binding phenomena. Accordingly, one important criterion in preparing peptide analogs according to the present invention is the respective chemical similarity of the side chains found in the peptide  
20 and any potential substitutes therefor appended to the core structure in the analog. In general, it is desired that the chemical functional group in the peptide of interest and its substitute in at least one of the peptide analogs be somewhat chemically dissimilar. Where the substitute is chemically  
25 dissimilar from the peptide side chain, it will generally be easier to elucidate the contribution, if any, of side chain to activity of the peptide.

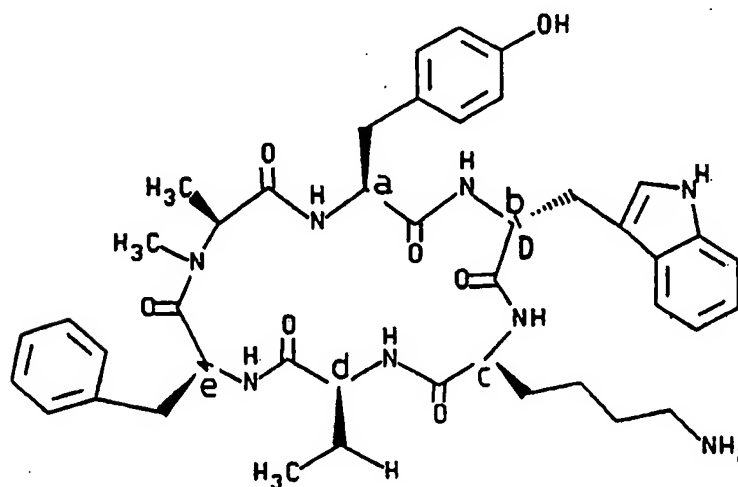
For example, it is believed that the bioactive conformation of somatostatin (also known as somatotropin  
30 release inhibiting factor or SRIF) includes a  $\beta$ -turn involving residues 7-10 ( $\text{Phe}^7$ - $\text{Trp}^8$ - $\text{Lys}^9$ - $\text{Thr}^{10}$ ). These four amino acids have been shown to be necessary and sufficient for receptor recognition and activation, so long as they are held in the proper orientation. Somatostatin accomplishes this proper  
35 orientation through its ten remaining amino acids and the cystine bridge contained therein. In a number of active cyclic hexapeptide analogs for somatostatin, proper

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orientation of the four amino acids is maintained via dipeptide segments. For example, the cyclic hexapeptide L-363,301 (structure (6a)), disclosed by Veber and Hirschmann, et al., *Life Sciences*, 1984, 34, 1371 and the cyclic  
5 hexapeptide MK-678 (structure (6b)), disclosed by Veber and Hirschmann, et al., *Nature*, 1981, 292, accomplish the proper orientation via the segments Phe-N-Me-Ala or Phe-Pro, respectively.



(6a)



(6b)

10

It is believed that the solution conformation of somatostatin involves a type I  $\beta$ -turn for residues 7-10 and that of the significantly more potent D-TRP diastereomer

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involves a type II'  $\beta$ -turn. While these two turns differ in the  $\Phi$  and  $\Psi$  angles of the amide backbone, they are believed to assume similar orientations of the side chains at the receptor. In the cyclic hexapeptides, the Phe-N-Me-Ala  
5 sequence and the Phe-Pro sequence are believed to be part of a type VI  $\beta$ -turn. Of particular significance is the high activity found for a modified retro-enantiomeric cyclic hexapeptide wherein the amide backbone is reversed. This demonstrates that proper side chain topography is important  
10 for activity but that the amide backbone may not be.

In accordance with the present invention, peptide analogs having structure (3) were further simplified by including only three adjacent side chains of the four amino acids of the  $\beta$ -turn. These side chains are attached to rigid  
15 frameworks devoid of peptide bonds. The frameworks were developed through molecular modeling to orient the side chains appropriately and/or to permit the receptor to induce the proper fit.

While a proper  $\beta$ -turn requires the fourth amino acid  
20 of the  $\beta$ -turn -- Thr in somatostatin and several cyclic hexapeptides and Val in the superactive cyclic hexapeptide -- it is believed that neither the Thr nor the Val side chains are required for binding. This assumption is based on the fact that highly active somatostatin analogs are known which  
25 have either Val, Thr, Ser,  $\alpha$ -aminobutyric acid, or Gly in the fourth position of the  $\beta$ -turn. Such non-specificity suggests a conformational rather than a binding role for that amino acid of the  $\beta$ -turn.

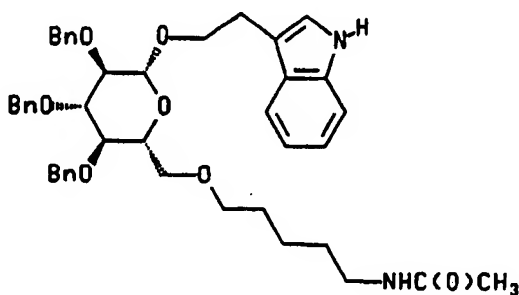
The phenylalanine residue in the dipeptide segments  
30 Phe-N-Me-Ala or Phe-Pro appears to add an important hydrophobic binding element. For this reason, the present synthetic analogs of somatostatin contain a corresponding aromatic residue. Increased hydrophobicity also should prove helpful in improving the duration of action and activity via  
35 oral administration of such compounds.

It is now believed that for the L-363,301 hexapeptide, structure (6a), the  $\beta$ -turn is important and the

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three groups extending from carbons a, b, and c -- benzyl, indole, and alkylamino, respectively -- are necessary for binding. Whereas the substituent at carbon d appears to be required to stabilize the  $\beta$ -turn rather than be required for binding, a benzyl group attached at carbon e of the skeleton is believed to be an important binding ligand which improves the activity of analogs.

It has now been discovered that a new class of therapeutic agents can be formulated having activity in a broad spectrum of utilities, especially those related to the G-protein-linked receptors. One member of the class is represented by structure (7).



(7)

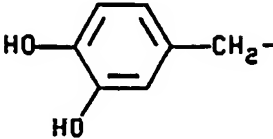
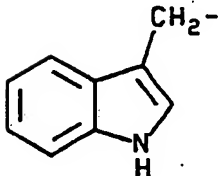
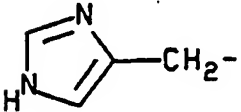
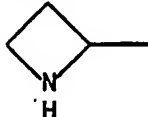
The calculated bond distances for structure (7) and the cyclic hexapeptide suggest close geometrical similarities. Furthermore, overlaying models of the designed structure (7) and the cyclic hexapeptide (6a) shows close correspondence of the important functionalities, particularly the phenylalanine, tryptophan and lysine residues.

The present invention, however, is not limited to embodiments wherein benzyl, indole, or alkylamino groups participate in binding. Participatory chemical functionality according to the present invention includes any of the wide variety of functional groups known in the art. The side chains of naturally-occurring amino acids provide examples of suitable participatory functionality. Representative participatory chemical functionality which may be contained within groups  $R_1$ - $R_5$  is set forth in Table 1. For example, one

- 14 -

or more of  $R_1$ - $R_5$  can have the structure  $Z-(CH_2)_y-$  or  $Z-O-$ , where  $y$  is from 0 to about 5 and  $Z$  is one of the side chains of Table 1.

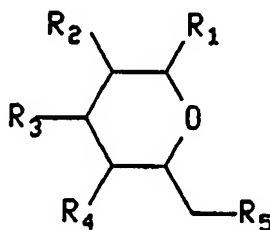
TABLE 1

5	$CH_3-$ $HO-CH_2-$ $C_6H_5-CH_2-$ $HO-C_6H_5-CH_2-$    $HS-CH_2-$	$CH_3-CH_2-S-CH_2-CH_2-HO-CH_2-CH_2-$ $CH_3-CH(OH)-$ $HO_2C-CH_2-NH_2C(O)-CH_2-$  $HO_2C-CH_2-CH_2-$ $NH_2C(O)-CH_2-CH_2-$ $(CH_3)_2-CH-$ $(CH_3)_2-CH-CH_2-$ $CH_3-CH_2-CH_2-$ $H_2N-CH_2-CH_2-CH_2-$ $H_2N-C(NH)-NH-CH_2-CH_2-CH_2-$ $H_2N-C(O)-NH-CH_2-CH_2-CH_2-$ $CH_3-CH_2-CH(CH_3)-$ $CH_3-CH_2-CH_2-CH_2-$ $H_2N-CH_2-CH_2-CH_2-CH_2-$
10	$HO_2C-CH(NH_2)-CH_2-S-S-CH_2-$ $CH_3-CH_2-$ $CH_3-S-CH_2-CH_2-$	



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In accordance with the present invention, non-peptide analogs preferably possess the general structure (3):



(3)

wherein:

5  $R_1$  is  $-O(CH_2)_nR_A$ ,  $-OC(O)(CH_2)_nR_A$ ,  $-(CH_2)_nR_A$ , or  $-C(O)(CH_2)_nR_A$  where  $R_A$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms and up to about 4 nitrogen atoms, or aryl having from about 6 to about 14 carbon atoms and up to about 4  
10 nitrogen atoms, and  $n$  is an integer from 0 to about 12;

at least one of  $R_2$ ,  $R_3$ , and  $R_4$ , independently, is  $-O(CH_2)_mR_B$ ,  $-OC(O)(CH_2)_mR_B$ ,  $-(CH_2)_mR_B$  or  $-C(O)(CH_2)_mR_B$  where  $R_B$  is  $-H$  or aryl, and  $m$  is an  
15 integer from 0 to about 5; and

$R_5$  is  $-O(CH_2)_pNHR_C$ ,  $-OC(O)(CH_2)_pNHR_C$ ,  $-O(CH_2)_pR_D$ ,  $-OC(O)(CH_2)_pR_D$ ,  $-(CH_2)_pNHR_C$ ,  $-C(O)(CH_2)_pNHR_C$ ,  $-(CH_2)_pR_D$  or  $-C(O)(CH_2)_pR_D$ , where:

$p$  is an integer from 0 to about 10;

20  $R_C$  is  $-R_E$  or  $-C(O)R_E$ ;

$R_D$  is  $-H$ ,  $-OR_E$ , or  $-C(O)R_E$ ;

$R_E$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms and up to about 4 nitrogen atoms, or aryl having from about 6 to about 14 carbon atoms and up to about 4 nitrogen atoms;

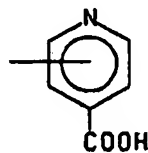
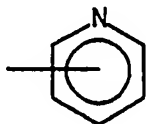
25

or a pharmaceutically acceptable salt thereof.

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It will be understood that the terms "alkyl" and "alkenyl" as employed herein are intended to include cyclic as well as straight chain moieties. In certain embodiments, the chemical structure and stereochemistry of the peptide  
5 analogs of the invention roughly correspond to that of  $\beta$ -D-glucose. Hence, the analogs can possess structures (4) and (5), with  $R_1$ - $R_5$  is defined as above.

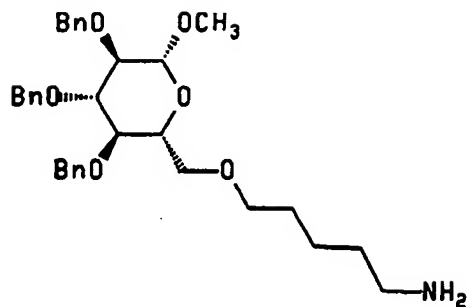
As will be recognized, the precise identity of  $R_1$ - $R_5$  depends intimately upon the peptide of interest whose  
10 biological and/or chemical activity is to be mimicked or inhibited. For example, in the case of compounds which are bound by G-protein-linked receptors such as the substance P receptor,  $R_A$  should be an aryl functional group, preferably an nitrogen-substituted aryl group such as pyridine or indole.  
15 More preferably,  $R_A$  is a 3-substituted indole. For such compounds, n should be 2 and  $R_B$  should be phenyl. The integer m should be zero or, preferably, 1. Also,  $R_5$  should be - $O(CH_2)_pNH_2$  or - $O(CH_2)_pNHR_C$ , where p is from about 2 to about 8, preferably 3 to about 6, more preferably 5.  $R_C$  can be, for  
20 example, a phenyl, benzyl or nitrogen heterocyclic moiety. Where substitution is possible at more than one position of these and other  $R_C$ , it is intended that the present invention include each of resulting peptide analogs. For example, it is intended that the invention include analogs wherein  $R_C$  is  
25 a pyridine or isonicotinic acid residue having one of the following structures:



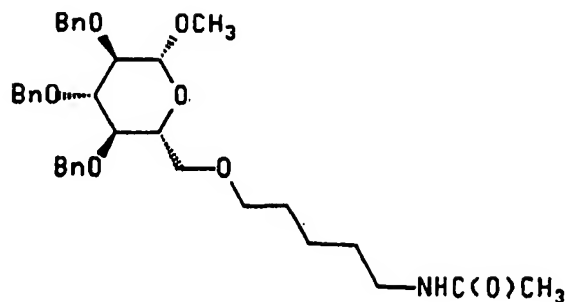
Preferably, however,  $R_C$  is  $-C(O)CH_3$ .

In general, preferred peptide analogs have  
30 structures (8) - (13).

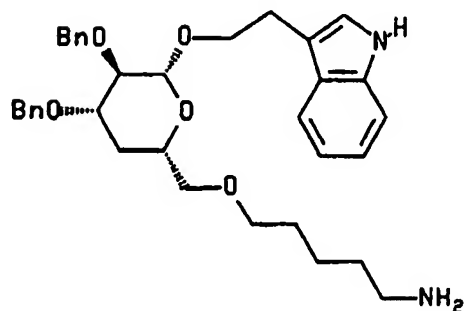
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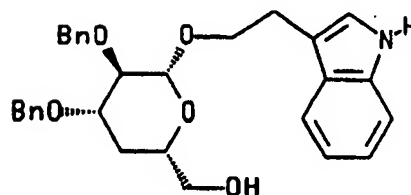
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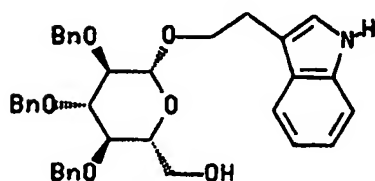
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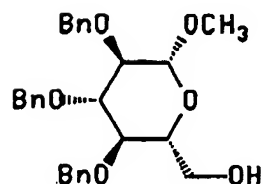
(10)



(11)



(12)



(13)

5 These peptide analogs are preferred to the extent that they selectively and effectively are bound by G-proteins-linked receptors such as the somatostatin receptor, the  $\beta$ -adrenergic receptor, and the substance P receptor. It will be recognized that the degree to which a compound is bound by a receptor is known as its binding activity or potency. The potency of a  
 10 compound commonly is expressed as its inhibitory concentration (IC), the concentration at which the compound is able to

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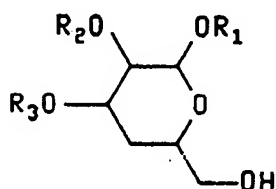
displace a predetermined portion -- typically 50% -- of another compound which is already bound by a particular receptor. In the case of ligand-binding studies, the compound that is displaced is a radioactive agonist or antagonist at the receptor under study. It is preferred in accordance with the present invention that a peptide analog possess a clinically effective  $IC_{50}$  in at least one mammal; that is, it should possess an  $IC_{50}$  which is low enough to inhibit binding of radioactive agonist or antagonist to a given G-protein linked receptor while causing a minimum of unacceptable side effects in the mammal. As will be recognized, clinically effective inhibitory concentrations vary depending on a number of factors, such as the pharmacokinetic characteristics and stability of the compound under study and thus must be determined empirically for each analog and each factor. For example, the clinically effective concentration for the somatostatin receptor is about 50-500 nM, but for the *in vitro* system the potency is, about 1-10 nM. In general, it is desired that the potency of a compound of the invention be as great as possible, preferably greater than or equal to the native hormone.

Selectivity or specificity is manifested for a compound of the present invention by its tendency to be bound by one particular G-protein-linked receptor but not other G-protein-linked receptors. In an experimental context, selectivity is manifested where a compound is bound by a particular receptor when placed in contact or close proximity with a medium containing at least one other receptor. Typically, specificity is expressed as a ratio of the potency or activity of a compound for two different receptors. Thus, a compound having an  $IC_{50}$  of 100  $\mu$ M for compound A and  $IC_{50}$  of 200  $\mu$ M for compound B can be said be two times more selective for compound A. In general, the selectivity of the peptide analogs of the present invention should be as great as possible. Selectivities greater than about 50-100 fold are preferred and selectivities greater than about 500 fold even more preferred.

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As can be seen, the present invention provides a wide variety of peptide analogs which effectively and selectively are bound by individual G-protein-linked receptors. The peptide analogs which bear amino groups are capable of forming salts with various inorganic and organic acids and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, sulfate, tartrate, tosylate, and undecanoate. The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is later removed in vacuo or by freeze drying. The salts also may be formed by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

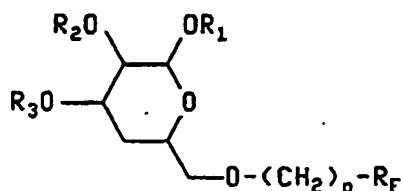
4-Deoxy, 6-alkoxyamino peptide analogs according to the invention (e.g., structures (10) and (11)) can be prepared by processes that include treating a 4-deoxy, 6-hydroxy glucopyranoside bearing hydroxyl protecting groups at positions 1, 2, and 3 with a base under conditions that do not remove the hydroxyl protecting groups. Preferred protected, 4-deoxy, 6-hydroxy glucopyranosides have structure (14):



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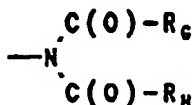
wherein  $R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting. Representative hydroxyl protecting groups include 2-(1-phenylsulfonyl)-indol-3-yl-ethyl or benzyl groups. Preferred protecting groups for a 1-position hydroxyl group include 2-(1-phenylsulfonyl)-indol-3-yl-ethyl groups. Preferred protecting groups for a 2- and/or 3-position hydroxyl include benzyl groups. It is particularly preferred that  $R_1$  is 2-(1-phenylsulfonyl)-indol-3-yl-ethyl and  $R_2$  and  $R_3$  are benzyl. Bases that can be used to abstract the 6-hydroxyl proton include 2,6-di-tert-butyl-4-methylpyridine and 2,4,6-trimethylpyridine. Those skilled in the art will be able to identify other useful bases through routine experimentation.

Following treatment with base, the nucleophilic 4-deoxy glucopyranoside is coupled with a protected alkylamine that bears a suitable leaving group, resulting in structure (15):

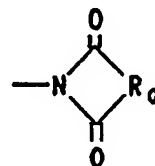


(15)

wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as above,  $R_F$  has structure (16) or (17),  $R_G$  and  $R_H$  are, independently, alkyl or alkenyl having from one to about 10 carbon atoms, and  $p$  is an integer from 0 to about 10.



(16)



(17)

Preferably, the protected glucopyranoside nucleophile is reacted with a compound having structure:

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where L is a leaving groups such as a O-trifluoromethane-sulfonyl group. Preferably,  $\text{R}_0$  and  $\text{R}_H$  comprise up to about 3  
 5 carbon atoms. It is particularly preferred that the amine function in structure  $\text{R}_f$  is protected as a phthalimide group.

Protected amine compounds (15) are converted to primary amines (18) through treatment with a suitable base under conditions that do not remove groups  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$ .  
 10 Suitable bases are those that can remove amide protecting groups from the amine function of structure  $\text{R}_f$  but cannot remove hydroxyl protecting groups  $\text{R}_1$ ,  $\text{R}_2$ , and  $\text{R}_3$ . Useful bases for deprotection reactions of this type include sodium methoxide and sodium ethoxide. Those skilled in the art will  
 15 be able to identify other useful bases through routine experimentation.

As will be recognized, the foregoing methods for preparing 4-deoxy, 6-alkoxyamino peptide analogs involve reaction of a glucopyranosidal O-nucleophile with a protected  
 20 alkylamine that bears a leaving group. It has been discovered that peptide analogs of this type generally cannot be prepared by a converse reaction, i.e., contacting a protected aminoalkoxide nucleophile with a glucopyranoside that bears a leaving group at its 6-position. While not wishing to be  
 25 bound by any particular theory, it is believed that steric bulk at the 4-position of the glucopyranoside stabilizes the reaction complex formed by the glucopyranoside and the alkylamine. In the absence of such steric bulk, the methods of the present invention can be employed to effect the desired  
 30 6-position linkage.

The present invention also provides compositions which comprise one or more peptide analogs. To the extent that the compositions comprise individual peptide analogs which are bound by certain receptors, the compositions will  
 35 likely also be bound by the same receptors. The analogs

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themselves may be present in the compositions in any of a wide variety of forms. For example, two or more peptide analogs may be merely mixed together or may be more closely associated through complexation, crystallization, or ionic or covalent  
5 bonding.

Those skilled in the art will appreciate that a wide variety of prophylactic, diagnostic, and therapeutic treatments may be prepared from the synthetic compounds and compositions of the invention, due in large part to the  
10 crossreactivity -- that is, agonism or antagonism -- of these moieties with one or more naturally-occurring peptides. For example, by administering an effective amount of a peptide analog, prophylactic or therapeutic responses can be produced in a human or some other type mammal. Preferred responses are  
15 produced by modulating -- that is, increasing, decreasing or otherwise modifying -- the activity of at least one G-protein-linked receptor. It will be appreciated that the production of prophylactic or therapeutic responses includes the initiation or enhancement of desirable responses, as well as  
20 the cessation or suppression of undesirable responses.

Certain preferred peptide analogs of the present invention exhibit significant substance P receptor-binding activity and therefore, are of value in the treatment of a wide variety of clinical conditions which are characterized  
25 by the presence of an excess of tachykinin, in particular substance P, activity. These include disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome;  
30 respiratory diseases such as bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract  
35 such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation;



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and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists  
5 for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

Compositions for use in the methods of this invention can be in the form of a solid, semisolid or liquid form and can include one or more of peptide analogs as an  
10 active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets,  
15 capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and  
20 other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes maybe used. The active ingredient is included in the pharmaceutical composition in an amount sufficient to produce  
25 the desired effect upon the process or condition of diseases.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and  
30 preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for  
35 tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk

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sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or  
5 dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of said  
10 compounds in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes.  
15 The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is  
20 also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

25 A compound of the invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes  
30 subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Dosage levels of the compounds within the present invention on the order from about 0.01 mg to about 50 mg per kilogram of body weight per day, preferably from about 0.1 mg  
35 to about 10 mg per kilogram body weight per day, are believed to be useful in the treatment of the above-indicated conditions (i.e., from about 0.7 mg to about 3.5 g per patient

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per day, assuming a 70 kg patient). In addition, the compounds of the present invention may be administered on an intermittent basis; i.e., at semi-weekly, weekly, semi-monthly or monthly intervals.

5           The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg  
10 to 5 mg of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 0.5 mg to about 500 mg of active ingredient. For topical administration in  
15 larger mammals a preparation containing a 1-3% concentration of active agent may be utilized.

          It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound  
20 employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. In some instances, dosage levels below the lower limit of the aforesaid range may  
25 be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

          Additional objects, advantages, and novel features  
30 of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting. Melting points were recorded on a Thomas Hoover Uni-Melt<sup>®</sup> melting point apparatus and are uncorrected. Proton and carbon NMR were recorded on a Bruker  
35 AM500 spectrometer. Chemical shifts are reported in  $\delta$  values relative to tetramethylsilane ( $\delta = 0$ ) for proton spectra and relative to chloroform- $d$  ( $\delta = 77.0$ ), acetone- $d_6$  ( $\delta = 29.8$ ) or

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methanol- $d_4$  ( $\delta = 49.0$ ) for carbon spectra. Coupling constants are given in hertz. Infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer and are reported in  $\text{cm}^{-1}$ . High resolution mass spectra were measured on a VG 70/70 micromass or VG ZAB-E spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Thin layer chromatography was performed on Merck Kieselgel 60  $F_{254}$  glass plates followed by visualization using a UV light or by staining with *p*-anisaldehyde solution (sugars), ninhydrin (primary amines), phosphomolybdic acid (secondary amines), or Erlich's reagent (indoles). Flash column chromatography was performed using Merck 60-200 mesh silica gel. All yields reflect purified isolated product after flash column chromatography or recrystallization unless otherwise noted.

#### 15 EXAMPLE 1

Preparation of Analog Having Structure (1), 2-(1*H*-Indol-3-yl)ethyl-6-O-(5-aminopentyl)-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside

##### A. 1-Bromo $\alpha$ -D glucose tetraacetate

20 Hydrobromic acid (30% in acetic acid, 11.85 ml, 55.4 mmol) was added to  $\beta$ -D-glucose pentaacetate (12.01 g, 30.8 mmol) at 0°C. After 10 minutes, the resulting solution was warmed to room temperature and stirred for 4 hours. The reaction mixture was slowly poured, with stirring, into ice water (250 ml) and was stirred until the product solidified. The product was collected by vacuum filtration and washed with cold water. The white solid was dissolved in carbon tetrachloride (60 ml) and washed with  $\text{H}_2\text{O}$  (1 x 20 ml), saturated aqueous  $\text{NaHCO}_3$  (3 x 20 ml, until pH = 7),  $\text{H}_2\text{O}$  (1 x 30 20 ml), dried with  $\text{CaCl}_2$ , and poured into cold petroleum ether (250 ml). After 30 min, the crystalline product was collected by vacuum filtration to give the target compound as a white solid (10.0 g, 80%).

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**B. N-phenylsulfonyl tryptophol****(a) 1-O-tert-butyldimethylsilyl-2-3-indolyl)ethanol**

To a solution of tryptophol (5.0 g, 31 mmol) in  
5 dimethylformamide (DMF, 30 ml) was added imidazole (4.64 g,  
68 mmol) and the reaction cooled to 0°C. To the cooled  
solution was added tert-butyldimethylsilyl chloride (5.14 g,  
34.1 mmol) and the reaction stirred at room temperature  
overnight. The reaction was diluted with ethyl acetate (100  
10 ml) and extracted with water (2 x 100 ml). The aqueous layer  
was extracted with ethyl acetate (1 x 200 ml.) The organic  
layers were combined and dried over anhydrous sodium sulfate.  
The solvents were removed under reduced pressure to yield a  
pale orange oil. Purification by flash column chromatography  
15 using 30% ether in petroleum ether yielded the target compound  
as a colorless oil (8.43 g, 99%).

**(b) 1-O-tert-butyldimethylsilyl-2-[3-(1-N-phenylsulfonyl)indolyl]ethanol**

Sodium hydride (1.91 g, 60% oil dispersion) was  
20 placed in a flame dried flask under argon. Dry DMF (64 ml)  
was added and the suspension cooled to 0°C. A solution of 1-  
O-tert-butyldimethylsilyl-2-3-indolyl)ethanol (8.43 g, 30.6  
mmol) in dry DMF (30 ml) was added to the suspension and the  
reaction stirred to room temperature for 30 minutes. After  
25 cooling to 0°C, benzenesulfonyl chloride (5.30 ml, 39.7 mmol)  
was added dropwise. The reaction was stirred at room  
temperature overnight. A solution of ammonium chloride (100  
ml) was added and the reaction was extracted with ether (3 x  
200 ml). The organic layers were combined, extracted with  
30 saturated sodium chloride, and dried over anhydrous sodium  
sulfate. Removal of the solvents under reduced pressure yield  
a pale yellow oil. Purification by flash column  
chromatography using 30% ether in petroleum ether yielded the  
target compound as a colorless oil (7.37 g, 79%).

**35 (c) N-phenylsulfonyl tryptophol**

To a solution of 1-O-tert-butyldimethylsilyl-2-[3-  
(1-N-phenylsulfonyl)indolyl]ethanol (6.6 g, 21.9 mmol) in

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tetrahydrofuran (THF, 100 ml) was added tetrabutylammonium fluoride (21 ml, 1 M in THF) and the solution stirred at room temperature overnight. The reaction was diluted with ethyl acetate (100 ml) and extracted with water (2 x 100 ml). The organic layer was re-extracted with saturated sodium chloride solution, dried over anhydrous sodium sulfate and the solvents removed under reduced pressure to yield a pale yellow oil. Purification by flash column chromatography using 40% ethyl acetate in petroleum ether yielded the target compound as a pale yellow oil which crystallized upon standing (4.00 g, 84%).

C. 2-(1-Phenylsulfonyl-3-yl)ethyl-2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranoside

To a suspension of crushed, flame dried 4 Å sieves (0.89 g) and silver (I) oxide (412 mg, 17.8 mmol) in 9 ml of dry hexane at room temperature, was added a solution of the above N-phenyl sulfonyl tryptophol (537 mg, 1.78 mmol) in 3 ml of dry benzene followed by a solution of 1-bromo  $\alpha$ -D glucose tetraacetate (804 mg, 1.95 mmol) in 3 ml of dry benzene. The reaction vessel was covered with aluminum foil and allowed to stir for 2 days at room temperature. Thin layer chromatography (TLC, 5% ether in methylene chloride) revealed product and some unchanged starting material. Silver (I) oxide (206 mg, 8.9 mmol) was added followed by 1 ml of dry benzene to loosen the suspension. The reaction as allowed to stir at room temperature an additional 2 days. The reaction suspension was filtered through celite. Concentration and crystallization from ethyl acetate/petroleum ether afforded 580 mg of the  $\beta$ -isomer of the target compound as a white solid. Concentration of the filtrate and flash chromatography (silica, 5% ether in methylene chloride) afforded a mixture of the  $\beta$ -isomer along with the  $\alpha$ -isomer and the corresponding ortho ester. Flash chromatography (silica, 70% ether in petroleum ether) on the mixture afforded an additional 134 mg of the  $\beta$ -isomer, bringing the yield to 64% (716 mg).

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**D. 2-(1-Phenylsulfonyl-indol-3-yl)ethyl- $\beta$ -D-glucopyranoside**

Sodium methoxide (221 mg, 4.09 mmol) was added to a suspension of 2-(1-phenylsulfonyl-3-yl)ethyl-2,3,4,6-tetra-  
5 O-acetyl- $\beta$ -D-glucopyranoside (3.22 g, 5.12 mmol) in 26 ml of methanol at room temperature. After 20 minutes, the resulting solution was diluted with 26 ml of methanol and neutralized by addition of amberlyst H<sup>+</sup> resin. The resin was quickly removed by filtration to avoid formation of the methyl  
10 glucoside. Concentration of the filtrate and flash chromatography (silica, 5:1:1 methylene chloride, methanol, acetone) afforded the target compound (2.09 g, 88%) as a white foam.

**E. 2-(1-Phenylsulfonyl-indol-3-yl) ethyl-6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside**

To a stirred solution of 2-(1-Phenylsulfonyl-indol-3-yl)ethyl- $\beta$ -D-glucopyranoside (7.11 g, 15.4 mmol) in 51 ml of dry DMF was added at room temperature, imidazole (2.93 g, 43.1 mmol) followed by tert-butyldiphenylsilyl chloride (5.58  
20 g, 21.6 mmol). The solution was maintained at 50°C for 24 hours. After removal of the DMF under reduced pressure, the reaction mixture was diluted with 250 ml of ethyl acetate and washed with H<sub>2</sub>O (1 x 100 ml), saturated aqueous NaCl (1 x 100 ml), and dried over magnesium sulfate. Concentration and  
25 flash chromatography (silica, 5% methanol in dichloromethane) provided pure target compound (9.15 g, 85%) as a white foam.

**F. 2-(1-Phenylsulfonyl-indol-3-yl)ethyl-2,3,4-tri-O-benzyl-6-O-tert-butyldiphenyl-silyl- $\beta$ -D-glucopyranoside**

To a stirred suspension of sodium hydride (323 mg, 60% oil dispersion, 808 mmol) in 5 ml of dry THF at 0°C was added a solution of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside (1.62 g, 2.31  
mmol) in 7 ml dry THF. After stirring 1 hour at room  
35 temperature, benzyl bromide (1.09 ml, 9.24 mmol) was added dropwise to the reaction mixture at 0°C followed by tetrabutylammonium iodide (85 mg, 0.23 mmol). After stirring

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3 days at room temperature, the suspension was treated with 3 ml of saturated aqueous ammonium chloride at 0°C. The resulting solution was diluted with 80 ml of ether and washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (1 x 30 ml), saturated aqueous NaCl (1 x 30 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 20% ether in petroleum ether) afforded the target compound (1.66 g, 74%) as a white foam.

10 G. 2-(1-Phenylsulfonyl-indol-3-yl)ethyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside

To a stirred solution of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-2,3,4-tri-O-benzyl-6-O-tert-butyl-diphenyl-silyl- $\beta$ -D-glucopyranoside (1.55 g, 1.60 mmol) in 8 ml of dry THF at room temperature was added tetrabutylammonium fluoride (1 M in THF, 2.4 ml, 2.4 mmol). After stirring 7 hours, the solution was diluted with 70 ml of ethyl acetate and washed with  $\text{H}_2\text{O}$  (1 x 30 ml) and saturated aqueous NaCl (1 x 30 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 30% ethyl acetate in petroleum ether) afforded the target compound (1.10 g, 94%) as a clear oil:  $R_f$  0.50 (40% ethyl acetate in petroleum ether);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J$  = 8.3 Hz, 1H), 7.82 (d,  $J$  = 7.9 Hz, 2H), 7.53 (s, 1H), 7.48-7.17 (m, 21H), 4.92 (d,  $J$  = 11.0 Hz, 1H), 4.86 (d,  $J$  = 10.9 Hz, 1H), 4.81 (d,  $J$  = 11.0 Hz, 1H), 4.74 (d,  $J$  = 11.0 Hz, 1H), 4.65 (d,  $J$  = 10.9 Hz, 1H), 4.62 (d,  $J$  = 11.0 Hz, 1H), 4.48 (d,  $J$  = 7.8 Hz, 1H), 4.20 (ddd,  $J$  = 9.4, 7.0, 7.0 Hz, 1H), 3.91-3.86 (m, 2H), 3.73 (dd,  $J$  = 3.5, 11.9 Hz, 1H), 3.63 (ddd,  $J$  = 9.0, 9.0, 18.0 Hz, 2H), 3.40 (ap. t,  $J$  = 8.0 Hz, 1H), 3.35 (ddd,  $J$  = 9.4, 4.2, 2.6 Hz, 1H), 3.04-2.93 (m, 2H), 2.06 (s, 1H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  138.48, 138.21, 138.13, 137.95, 135.09, 133.60, 130.92, 129.10, 128.40, 128.30, 128.25, 128.22, 127.98, 127.90, 127.82, 127.76, 127.55, 126.58, 124.72, 123.57, 123.12, 119.61, 119.31, 113.66, 103.59, 84.39, 82.25, 77.37, 75.56, 75.16, 74.99, 74.75, 68.60, 61.77, 25.57; IR (thin film) 3480 (w), 3065 (w), 3035 (w), 2920 (m), 2878 (m), 1498 (w), 1450 (s).



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1365 (s), 1280 (w), 1220 (m), 1176 (s), 1123 (s), 1090 (s),  
1073 (s), 1030 (s), 750 (s), 700 (s)  $\text{cm}^{-1}$ ; UV-Vis ( $c = 9.21 \times 10^{-5}$ , acetonitrile)  $\lambda_{\text{max}}$  254.0 ( $\epsilon = 2.81 \times 10^3$ ), 211.6 ( $\epsilon = 3.19 \times 10^4$ ) nm; HRMS  $m/e$  calculated for  $\text{C}_{43}\text{H}_{43}\text{NO}_6\text{S}$  ( $M+H$ ):  
5 734.2774, found 734.2743;  $[\alpha]_D^{20} -13.3^\circ$  ( $c = 0.135$ , acetonitrile); Analysis calculated for  $\text{C}_{43}\text{H}_{43}\text{NO}_6\text{S}$ : C, 70.37; H, 5.91; found: C, 70.30; H, 6.08.

H. 2-(1Phenylsulfonyl-indol-3yl)ethyl-2,3,4-tri-O-benzyl-6-O-trifluoromethylsulfonyl- $\beta$ -D-glucopyranoside  
10

To a stirred solution of 2-(1-phenylsulfonyl-indol-3yl)ethyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside (196 mg, 0.27 mmol) in 2.7 ml of dry dichloromethane at  $-78^\circ\text{C}$  was added 2,6-di-tert-butyl-4-methyl pyridine (880 mg, 0.427 mmol) followed  
15 by triflic anhydride (58  $\mu\text{l}$ , 0.347 mmol). After stirring 15 minutes at  $-78^\circ\text{C}$ , the mixture was warmed to room temperature over 20 minutes, and then poured into saturated aqueous  $\text{NaHCO}_3$  (20 ml) and extracted with ethyl acetate (60 ml). The organic layer was washed with saturated aqueous  $\text{NaHCO}_3$  (3 x 20 ml);  
20 saturated aqueous  $\text{NaCl}$  (1 x 20 ml) and dried over magnesium sulfate. Concentration provided the crude target compound, which used in the next step without purification.

I. N-trifluoroacetyl-5-amino pentanol

To a solution of 5-amino pentanol (1 g, 9.69 mmol)  
25 in methanol (25 ml, 0.4 M) at  $0^\circ\text{C}$  was added triethylamine (2 ml, 1.5 equiv, 10 mmol) followed by very slow dropwise addition of trifluoroacetic anhydride (1.8 ml, 1.3 equiv, 12.5 mmol). The reaction mixture was warmed to room temperature and stirred overnight. TLC (5%  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) stained with  
30 ninhydrin revealed starting material; TLC stained with phosphomolybdic acid revealed product. The reaction mixture was cooled to  $0^\circ\text{C}$  and triethylamine (1.3 ml, 1 equiv, 9.69 mmol) was added followed by trifluoroacetic anhydride (1 ml, 0.8 equiv.). The reaction mixture was warmed to room  
35 temperature and stirred an additional night. Concentration and flash chromatography (silica, 60% EtOAc/petroleum ether) afforded the target compound (1.7 g, 85%).

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J. 2-(1-Phenylsulfonyl-indol-3yl)ethyl-2,3,4 tri-O-benzyl-6-O-(N-trifluoroacetyl-5-aminopentyl)- $\beta$ -D-glucopyranoside

To a stirred suspension of sodium hydride (123 mg, 0.307 mmol, 60% oil dispersion) in 17 ml of dry THF at 0°C was added a solution of N-trifluoroacetyl-5-amino pentanol (265 mg, 1.3 mmol) in 10 ml of dry THF. After stirring 10 minutes at 0°C, the suspension was warmed to room temperature, stirred for 1 hour, and cooled to 0°C. A solution of the above 2-(1-phenylsulfonyl-indol-3yl)ethyl-2,3,4-tri-O-benzyl-6-O-trifluoromethylsulfonyl- $\beta$ -D-glucopyranoside (theoretically 0.27 mmol) in 16 ml of dry dichloromethane was added slowly dropwise. The reaction mixture was stirred at 0°C for 30 minutes and then warmed to room temperature. After stirring 24 hours, TLC (2% methanol in dichloromethane) revealed diprotected target compound and a minor amount of monoprotected product. The reaction mixture was cooled to 0°C and quenched with 10 ml of saturated aqueous ammonium chloride. The resulting mixture was diluted with ethyl acetate (150 ml) and washed with H<sub>2</sub>O (1 x 50 ml), saturated aqueous NaCl (1 x 50 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 2% methanol in dichloromethane) yielded a mixture of diprotected target compound and monoprotected product which was used as a mixture in the next step.

K. Structure (1), 2-(1H-Indol-3yl)ethyl-6-O-(5-aminopentyl)-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside

To a stirred solution of the mixture of step J, above, (theoretically 0.27 mmol) in 6 ml of ethanol at room temperature was added a solution of 5M NaOH (2 ml, 10 mmol). The solution was heated to reflux for 2 hours. The solvents were removed under reduced pressure. The reaction mixture was diluted with ethyl acetate (40 ml) and washed with H<sub>2</sub>O (1 x 15 ml), saturated aqueous NaCl (1 x 15 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 5% methanol in dichloromethane provided structure (1)

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(150 mg, 83% for 3 steps) as an oil: Rf 0.26 (7% methanol in dichloromethane); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.33-7.04 (m, 19H), 4.90 (d, J = 10.9 Hz, 1H), 4.85 (d, J = 11.1 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.64 (d, J = 11.0 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.48 (d, J = 7.8 Hz, 1H), 4.21 (ddd, J = 9.4, 6.7, 6.7 Hz, 1H), 3.89 (ddd, J = 9.4, 7.3, 7.3 Hz, 1H), 3.64 (dd, J = 9.0, 9.0 Hz, 1H), 3.56 (t, J = 6.4 Hz, 2H), 3.51-3.47 (m, 1H), 3.42 (t, J = 9.2 Hz, 2H), 3.11 (t, 7.0 Hz, 2H), 2.96 (dd, J = 12.3, 2.6 Hz, 1H), 2.66 (dd, J = 12.3, 7.8 Hz, 1H), 2.62-2.54 (m, 2H), 1.93 (s, 2H), 1.54-1.44 (m, 4H), 1.38-1.32 (m, 2H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 138.57, 138.49, 138.14, 136.17, 128.43, 128.36, 128.29, 128.02, 127.88, 127.82, 127.60, 127.56, 127.50, 122.14, 121.96, 119.30, 118.68, 112.60, 111.13, 103.67, 84.61, 82.45, 79.70, 77.20, 75.68, 74.99, 74.73, 73.82, 70.25, 62.63, 50.52, 49.59, 32.36, 29.28, 25.86, 23.31; IR (thin film) 3420(w), 3300(w), 3063(w), 3033(w), 2938(m), 2860(m), 1495(w), 1455(m), 1360(m), 1210(w), 1072(s), 1026(m), 910(w), 538(s), 495(s) cm<sup>-1</sup>; UV-Vis (c=1.14x10<sup>-4</sup>, acetonitrile) λ<sub>max</sub> 289.6 (ε=4.17 x 10<sup>3</sup>), 280.8 (ε=4.97 x 10<sup>3</sup>), 220.0 (ε=2.4 x 10<sup>4</sup>) nm; HRMS m/e calc'd C<sub>42</sub>H<sub>50</sub>N<sub>2</sub>O<sub>6</sub> (M + H): 679.373; found 679.370; [α]<sub>D</sub><sup>20</sup>+3.2° (c=0.31, acetonitrile).

## EXAMPLE 2

### 25 Preparation of Analog Having Structure (7), 2-(1H-Indol-3yl)ethyl-6-O-(5-acetamidopentyl)-2,3,4-tri-O-benzyl-β-D-glucopyranoside

To a solution of 5-amino pentanol (0.75 g, 7.27 mmol) in methanol (15 ml, 0.5 M) at 0°C was added triethylamine (1.62 ml, 1.6 equiv, 11.6 mmol) followed by acetic anhydride (0.891 ml, 1.3 equiv, 9.45 mmol). The reaction mixture was warmed to room temperature and stirred overnight. TLC (8% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) stained with ninhydrin revealed starting material. Triethylamine (1.6 ml, 1.6 equiv, 11.6 mmol) was added to room temperature followed by acetic anhydride (0.9 ml, 1.3 equiv, 9.45 mmol) and the reaction

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mixture was stirred an additional night. Concentration and flash chromatography (silica, 7% CH<sub>3</sub>OH/EtOAc) afforded N-CH<sub>3</sub>CO-5-amino-pentanol (1 g, 100%).

Sodium hydride (0.108 g, 60% suspension in oil, 0.307 mmol, 2.2 equiv. compared to N-CH<sub>3</sub>CO-5-amino-pentanol) was quickly weighed into a flame dried flask under argon. THF (20 ml, 0.01 M compared to moles of the triflate) was added and the resulting suspension was cooled to 0°C. A solution of N-CH<sub>3</sub>CO-5-amino-pentanol (0.108 g, 0.22 moles, 5 equiv) in 5 ml of THF was added dropwise and then warmed to room temperature for 1 hour. The resulting suspension was cooled to 0°C and a solution of the 2-(1-phenylsulfonyl-indol-3-yl)ethyl-2,3,4 tri-O-benzyl-β-D-glucopyranoside triflate prepared in Example 1, step H (assumed 0.245 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml, CH<sub>2</sub>Cl<sub>2</sub>:THF=3:5) was added slowly dropwise and stirred for 1 hour. The reaction mixture was warmed to room temperature and stirred overnight. TLC (3% methanol in dichloromethane) revealed no starting material and a major and minor product very close in R<sub>f</sub>. Both were collected since the minor product is deprotected indole and the mixture is transformed to the same product in the next step. The reaction mixture was cooled to 0°C and quenched with aqueous saturated ammonium chloride. The reaction mixture was poured into EtOAc and washed 1 x H<sub>2</sub>O and 1 x aqueous saturated NaCl. The organic layer was dried with MgSO<sub>4</sub> and filtered. Concentration and flash chromatography (silica, 3% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) yielded the major and minor product which was used as a mixture in the next step.

To a solution of the above mixture (assumed 0.245 mmol) in ethanol (4 ml, 0.05 M) at room temperature was added 2 ml of 5 M NaOH and the cloudy reaction mixture was heated to reflux for 2 hours. The reaction solvent was concentrated, diluted with EtOAc, and washed 1 x H<sub>2</sub>O and 1 x aqueous saturated NaCl. The organic layer was dried with MgSO<sub>4</sub> and filtered. Concentration and flash chromatography (silica, 4% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) yielded structure (7), 2-(1H-indol-3yl)ethyl-6-O-(5-acetamidopentyl)-2,3,4-tri-O-benzyl-β-D-glucopyranoside.

**EXAMPLE 3**

**Preparation of Analog Having Structure (2), 2-(1H-indol-3-yl)ethyl-6-O-(5-aminopentyl)-2,4-di-O-benzyl-3-deoxy- $\beta$ -D-glucopyranoside**

5           **A. Methyl 2-O-benzoyl-4,6-O-isopropylidene- $\alpha$ -D-glucopyranoside**

To a stirred solution of methyl 2-4,6-O-isopropylidene- $\alpha$ -D-glucopyranoside (28.8 g, 123 mmol) in 410 ml of dichloromethane at 0°C was added triethylamine (25.7 ml, 185 mmol) followed by benzoic anhydride (30.73 g, 135 mmol). The solution was warmed to room temperature and stirred for 24 hours. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (500 ml) and washed with H<sub>2</sub>O (1 x 200 ml), a saturated aqueous NaCl (1 x 15 200 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 25% ethyl acetate in petroleum ether) provided the target compound (33.4 g, 80%) as a white form.

20           **B. Methyl 2-O-benzoyl-3-O-(methylthio)thiocarbonyl-4,6-O-isopropylidene- $\alpha$ -D-glucopyranoside**

To a stirred solution of methyl 2-O-benzoyl-4,6-O-isopropylidene- $\alpha$ -D-glucopyranoside (1 g, 2.95 mmol) in 10 ml of dry THF at -78° was added sodium bis(trimethyl silyl)amide 25 (1 M solution in THF, 3.54 ml, 3.4 mmol) followed immediately by carbon disulfide (248  $\mu$ l, 4.13 mmol). After stirring the solution for 15 minutes at -78°C, methyl iodide (550  $\mu$ l, 11.8 mmol) was added. The solution was stirred at -78°C an additional 10 minutes and then brought to room temperature. 30 After stirring 30 minutes, the reaction was quenched with 2 ml of H<sub>2</sub>O, diluted with 60 ml of ether, washed with H<sub>2</sub>O (1 x 30 ml), saturated aqueous NaCl (1 x 30 ml) and dried over magnesium sulfate. Removal of the solvent yielded crude xanthate (1.52 g crude). A 1.28 g aliquot of the crude 35 xanthate was used in the next step without further purification. The remaining 0.24 g of target compound was

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purified by flash chromatography (silica, 20% ether in petroleum ether) to yield a white solid.

**C. Methyl 2-0-benzoyl-3-deoxy-4,6-0-isopropylidene- $\alpha$ -D-glucopyranoside**

5 To a solution of crude methyl 2-0-benzoyl-3-0-(methylthio)thiocarbonyl-4,6-0-isopropylidene- $\alpha$ -D-glucopyranoside (1.28 g, 2.48 mmol theoretically) in 10 ml of dry toluene at room temperature was added 2,2'-azobisisobutyro-nitrile (AIBN, 40 mg) followed by tributyl tin  
10 hydride (2 ml, 7.48 mmol). The reaction was heated to reflux for 2 hours. The toluene was removed under reduced pressure. The resulting oil was dissolved in 60 ml of acetonitrile and washed with petroleum ether (3 x 20 ml). Concentration of the acetonitrile and flash chromatography (silica, 10% ethyl  
15 acetate in petroleum ether) yielded pure target compound (585 mg, 73% from 3b) as a clear oil.

**D. Methyl 3-deoxy- $\alpha$ -D-glucopyranoside**

To a stirred suspension of methyl 2-0-benzoyl-3-deoxy-4,6-0-isopropylidene- $\alpha$ -D-glucopyranoside (520 mg, 1.61  
20 mmol) in 8 ml of methanol at room temperature was added sodium methoxide (70 mg, 1.29 mmol). After stirring 2h, the benzoyl group had been completely removed as evidenced by TLC. Amberlyst H<sup>+</sup> resin was added and the mixture stirred for 1 hours until the generation of the free triol was completed as  
25 evidenced by TLC. After filtration, the solvents were removed under reduced pressure. Flash chromatography (silica, 10% methanol in methylene chloride) yielded pure target compound (286 mg, 100%) as an oil.

**E. Methyl 2,4,6-tri-0-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside**

30 To a stirred solution of methyl 3-deoxy- $\alpha$ -D-glucopyranoside (535 mg, 3.0 mmol) in 10 ml of methylene chloride at 0° C was added triethylamine (2.92 ml, 21.0 mmol), followed by acetic anhydride (1.41 ml, 15.0 mmol) and then 4-  
35 dimethyl amino pyridine (37 mg, 0.30 mmol). The solution was warmed to room temperature. After stirring 7 hours, the solution was diluted with 60 ml of ethyl acetate and washed

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with H<sub>2</sub>O (1 x 30 ml), saturated aqueous NaCl (1 x 30 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 40% ether in petroleum ether) provided pure target compound (820 mg, 90%) as a clear oil.

5                   F.    1,2,4,6-tetra-0-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside

To a stirred solution of methyl 2,4,6-tri-0-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside (127 mg, 0.41 mmol) in 3 ml of acetic anhydride at 0°C was added boron trifluoride etherate  
10 (15  $\mu$ l, 0.12 mmol). The solution was warmed to room temperature, stirred for 1.25 hours, and poured into 30 ml of an ice cold saturated solution of NaHCO<sub>3</sub> and extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (2 x 40 ml), saturated  
15 aqueous NaCl (1 x 40 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 30% ethyl acetate in petroleum ether) provided the target compound (133 mg, 96%) as an oil.

20                   G.    Bromo    2,4,6-tri-0-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside

Hydrobromic acid (30% in acetic acid solution, 3 ml, 14.0 mmol) was added to 1,2,4,6-tetra-0-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside (750 mg, 2.26 mmol) at 0°C. After 10 minutes, the resulting solution was warmed to room temperature for 30  
25 minutes. The solution was then diluted with ether (20 ml) and poured into a mixture of ice and a saturated solution of NaHCO<sub>3</sub> (25 ml). An additional 30 ml of ether was added and the layers were separated. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 25 ml), H<sub>2</sub>O (1 x 25 ml),  
30 saturated aqueous NaCl (1 x 25 ml), and dried over magnesium sulfate. Removal of the solvent provided crude target compound, which was used in the next step without further purification.

35                   H.    2-(1-Phenylsulfonyl-indol-3-yl)ethyl-2,4,6-tri-0-acetyl-3-deoxy- $\beta$ -D-glucopyranoside

To a stirred suspension of flame dried 4A sieves (1.33 g) in 11 ml of dry hexane at room temperature was added

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a solution of N-benzenesulfonyltryptophol (1.20 g, 4.0 mmol) in 4 ml of dry benzene. Next, a solution of the above bromo 2,4,6-tri-O-acetyl-3-deoxy- $\alpha$ -D-glucopyranoside(theoretically 2.26 mmol) in 4 ml of dry benzene was added, followed by  
5 silver(I)oxide (523 mg, 2.26 mmol). The reaction vessel was covered with aluminum foil and the suspension stirred for 3 days. After filtration through celite, concentration of the filtrate under reduced pressure and flash chromatography (silica, 10:1 methylene chloride:ether) provided pure target  
10 compound (781 mg, 60%) as a white foam.

I. 2-(1-Phenylsulfonyl-indol-3-yl)ethyl-3-deoxy- $\beta$ -D-glucopyranoside

To a stirred suspension of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-2,4,6-tri-O-acetyl-3-deoxy- $\beta$ -D-glucopyranoside (735 mg, 1.28 mmol) in 6.4 ml of methanol was  
15 added sodium methoxide (55.2 mg, 1.02 mmol) at room temperature. After 90 minutes, the resulting solution was diluted with 6.4 ml of methanol (6.4 ml) and neutralized by addition of amberlyst H<sup>+</sup> resin. The resin was quickly removed  
20 by filtration to avoid formation of the methyl glucoside. Concentration of the filtrate and flash chromatography (silica, 12:1:1 methylene chloride, acetone, methanol) afforded pure target compound (498 mg, 87%) as a white solid.

J. 2-(1-Phenylsulfonyl-indol-3yl)ethyl-3-deoxy-6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside  
25

To a stirred solution of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-3-deoxy- $\beta$ -D-glucopyranoside (779 mg, 1.74 mmol) in 17 ml of dry DMF (at room temperature) was added imidazole (260 mg, 3.83 mmol) followed by tert-butyldiphenylsilyl  
30 chloride (541  $\mu$ l, 2.09 mmol). The solution was stirred at 50°C for 24 hours. The reaction mixture was diluted with 250 ml of ethyl acetate and washed with H<sub>2</sub>O (2 x 100 ml), saturated aqueous NaCl (1 x 100 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 3%  
35 methanol in methylene chloride) provided pure target compound (1.04 g, 87%) as a white foam.



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K. 2-(1-Phenylsulfonyl-indol-3yl)ethyl-3-deoxy-  
2,4-di-O-benzyl-6-O-tert-butyldiphenylsilyl- $\beta$ -  
D-glucopyranoside

To a stirred suspension of sodium hydride (4.63  
5 mmol, 185 mg, 60% oil dispersion) in 5 ml of dry THF at 0°C  
was added a solution of 2-(1-phenylsulfonyl-indol-3yl)ethyl-3-  
deoxy-6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside (1.27  
g, 1.85 mmol) in 10 ml of dry THF. After 10 minutes, the  
mixture was warmed to room temperature. After stirring 1  
10 hour, the suspension was cooled to 0°C and benzyl bromide  
(5.55 mmol, 660  $\mu$ l) was added followed by tetrabutylammonium  
iodide (68 mg, 0.185 mmol). The mixture was warmed to room  
temperature and stirred for 3 days. The reaction was then  
quenched with 3 ml of aqueous saturated ammonium chloride at  
15 0°C. The resulting solution was diluted with 80 ml of ether  
and washed with H<sub>2</sub>O (2 x 30 ml), saturated aqueous NaCl (1 x  
30 ml), and dried over magnesium sulfate. Concentration under  
reduced pressure and flash chromatography (silica, 25% ether  
in petroleum ether) provided pure target compound (760 mg,  
20 47%) as a white foam.

L. 2-(1-phenylsulfonyl-indol-3yl)ethyl-3-deoxy-  
2,4-di-O-benzyl- $\beta$ -D-glucopyranoside

To a stirred solution of 2-(1-phenylsulfonyl-indol-  
3yl)ethyl-3-deoxy-2,4-di-O-benzyl-6-O-tert-butyldiphenylsilyl-  
25  $\beta$ -D-glucopyranoside (675 mg, 0.780 mmol) in 10 ml of dry THF  
was added tetrabutylammonium fluoride (1 M solution in THF,  
1.17 mmol, 1.17 ml) at room temperature. After stirring 2  
hours, the solution was diluted with 80 ml of ethyl acetate  
and washed with H<sub>2</sub>O (1 x 30 ml), saturated aqueous NaCl (1 x  
30 30 ml), and dried over magnesium sulfate. Concentration and  
flash chromatography (silica, 60% ether in petroleum ether)  
afforded pure target compound (445 mg, 91%) as an oil.

M. 2-(1-Phenylsulfonyl-indol-3yl)ethyl-3-deoxy-  
2,4-di-O-benzyl-6-O-trifluoromethylsulfonyl- $\beta$ -  
35 D-glucopyranoside

To a stirred solution of 2-(1-phenylsulfonyl-indol-  
3yl)ethyl-3-deoxy-2,4-di-O-benzyl- $\beta$ -D-glucopyranoside (360 mg,

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0.575 mmol) in 3 ml of dichloromethane at -78°C was added, 2.6 di-tert-butyl-4-methylpyridine (189 mg, 0.92 mmol) followed by triflic anhydride (126  $\mu$ l, 0.748 mmol). After stirring 20 minutes at -78°C, the mixture was allowed to warm to room temperature over 20 minutes. The suspension was poured into aqueous saturated NaHCO<sub>3</sub> (15 ml) and extracted with ethyl acetate (1 x 35 ml). The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 15 ml), saturated aqueous NaCl (1 x 15 ml) and dried over magnesium sulfate. Concentration afforded crude target compound as an oil which was used in the next step without further purification.

N. 2-(1-Phenylsulfonyl-3-yl)ethyl-2,4-di-O-benzyl-3-deoxy-6-O-(N-trifluoroacetyl-5-aminopentyl)- $\beta$ -D-glucopyranoside

To a stirred suspension of sodium hydride (8.63 mmol, 345 mg, 60% dispersion in oil) in 20 ml of dry THF at 0°C was added a solution of N-trifluoro acetyl 5-amino pentanol (687 mg, 3.45 mmol) in 16 ml of dry THF. After stirring 10 minutes at 0°C, the suspension was allowed to warm to room temperature and stir for 90 minutes. The reaction mixture was then cooled to 0°C and a solution of crude triflate of step M (theoretically 0.575 mmol) in 22 ml of dry dichloromethane was added. The suspension was stirred for 30 minutes at 0°C and then warmed to room temperature. After stirring for an additional 24 hours, the reaction was quenched at 0°C with 10 ml of saturated aqueous ammonium chloride. The resulting mixture was diluted with ethyl acetate (200 ml) and washed with H<sub>2</sub>O (1 x 75 ml), saturated aqueous NaCl (1 x 75 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, eluted column 5 times with 1% methanol in methylene chloride then 2% methanol in methylene chloride) afforded the target compound (392 mg) as a white foam which was used without further purification in the next step.

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O. Structure (2), 2-(1H-indol-3-yl)ethyl-6-O-(5-aminopentyl)-2,4-di-O-benzyl-3-deoxy- $\beta$ -D-glucopyranoside.

To a stirred solution of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-2,4-di-O-benzyl-3-deoxy-6-O-trifluoromethylsulfonyl- $\beta$ -D-glucopyranoside (392 mg, theoretically 0.575 mmol) in 6 ml of ethanol at room temperature was added a solution of 5 M NaOH (1 ml, 5 mmol). The solution was allowed to reflux for 2 hours. The solvents were removed under reduced pressure, and the reaction mixture was diluted with dichloromethane (75 ml) and washed with aqueous HCl (25 ml, 5 mmol). The water layer was re-extracted with dichloromethane (2 x 75 ml). The combined organic layers were washed with saturated aqueous NaCl (2 x 25 Ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 8% methanol in dichloromethane) afforded the pure product, structure (7) (172 mg, 52% for 3 steps) as an oil.  $R_f$  0.22 (8% methanol in dichloromethane);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (s, 1H), 7.57 (d,  $J$  = 7.7 Hz, 1H), 7.31-7.23 (m, 10H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 1H), 7.04 (d,  $J$  = 2.9 Hz, 1H), 4.71 (d,  $J$  = 11.8 Hz, 1H), 4.57 (d,  $J$  = 11.7 Hz, 1H), 4.56 (d,  $J$  = 11.9 Hz, 1H), 4.46 (d,  $J$  = 7.5 Hz, 1H), 4.40 (d,  $J$  = 11.5 Hz, 1H), 4.20 (ddd,  $J$  = 13.8, 9.4, 6.8 Hz, 1H), 3.87 (ddd,  $J$  = 14.9, 9.3, 7.4 Hz, 1H), 3.55-3.50 (m, 3H), 3.32-3.26 (m, 2H), 3.11 (t,  $J$  = 7.2 Hz, 2H), 3.02 (dd,  $J$  = 12.4, 2.9 Hz, 1H), 2.68 (dd,  $J$  = 12.4, 8.1 Hz, 1H), 2.67-2.57 (m, 2H), 2.50 (ddd,  $J$  = 12.3, 4.8, 4.8 Hz, 1H), 2.20 (s, 3H), 1.57-2.44 (m, 5H), 1.36-1.30 (m, 2H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  138.61, 137.92, 136.14, 128.41, 128.27, 127.79, 127.70, 127.53, 127.49, 122.18, 121.84, 119.18, 118.67, 112.56, 111.12, 105.22, 105.18, 76.53, 75.14, 74.28, 72.69, 70.99, 69.91, 62.45, 50.69, 49.49, 34.86, 32.28, 29.16, 25.80, 23.27; IR (thin film) 3325(m), 3065(w), 3035(w), 3015(w), 2940(s), 2870(s), 1500(w), 1458(m), 1354(w), 1220(w), 1076(s), 1030(m), 745(s), 700(s)  $\text{cm}^{-1}$ ; UV-Vis ( $c=6.5 \times 10^{-3}$  acetonitrile)  $\lambda_{\text{max}}$  281.2 ( $\epsilon=6.2 \times 10^3$ ), 218.8 ( $\epsilon=3.62 \times 10^4$ ) nm; HRMS m/e calc'd for

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$C_{35}H_{44}N_2O_5$  (M + H): 573.3315, found 573.3314;  $[\alpha]D^{20} + 16.7^\circ$  (c = 0.15, acetonitrile).

**EXAMPLE 4**

Preparation of Analog Having Structure (13), Methyl 2,3,4-tri-  
5 O-benzyl-6-O-(N-trifluoroacetyl-5-aminopentyl)- $\beta$ -D-glucopyranoside

A. Methyl 6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside

To a stirred solution of methyl  $\beta$ -D-glucopyranoside  
10 (5 g, 25.7 mmol) in 51 ml of dry DMF was added at room temperature imidazole (5.46 g, 80.2 mmol) followed by tert-butyldiphenyl-silyl chloride (11.3 ml, 43.4 mmol). The solution was heated to 50°C for 24 hours and the DMF was removed under reduced pressure. The reaction mixture was  
15 diluted with 200 ml of ethyl acetate and washed with H<sub>2</sub>O (1 x 100 ml), saturated aqueous NaCl (1 x 100 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 4% methanol in dichloromethane) provided pure target compound (9.82 g, 88%) as a white foam.

20 B. Methyl 6-O-tert-butyldiphenylsilyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside

To a stirred suspension of sodium hydride (1.67 g, 41.6 mmol) in 100 ml of dry THF was added at 0°C a solution of methyl 6-O-tert-butyldiphenylsilyl- $\beta$ -D-glucopyranoside (4.0  
25 g, 9.25 mmol) in 50 ml of dry THF. After 5 minutes, the suspension was warmed to room temperature and stirred for 1 hour. Benzyl bromide (5.50 ml, 46.2 mmol) was added at room temperature followed by tetrabutylammonium iodide (341 mg, 0.93 mmol). The suspension was warmed to 50°C and stirred for  
30 4 days. After quenching with 40 ml of saturated aqueous ammonium chloride, the resulting mixture was diluted with ether (600 ml) and washed with H<sub>2</sub>O (2 x 200 ml), saturated aqueous NaCl (1 x 200 ml), and dried over magnesium sulfate. Concentration and flash chromatography (silica, 10% ether in  
35 petroleum ether) provided pure target compound (4.48 g, 69%) as a clear oil.

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C. Methyl 2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside

To a stirred solution of methyl 6-O-tert-butyl-diphenylsilyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside (2.81 g, 3.98 mmol) in dry THF (40 ml, 0.1 M) at room temperature was added tetrabutyl ammonium fluoride (4.37 ml, 4.37 mmol, 1 M solution in THF). After stirring for 3 hours, the reaction solution was diluted with ethyl acetate (300 ml) and washed with water (1 x 100 ml) and saturated aqueous NaCl (1 x 100 ml), and dried with magnesium sulfate. Concentration and flash chromatography (silica, 50% ether in petroleum ether) provided pure target compound (1.62 g, 88%) as a white solid.

D. Methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethylsulfonyl- $\beta$ -D-glucopyranoside

To a stirred solution of methyl 2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside (800 mg, 1.71 mmol) in 8.55 ml of dry dichloromethane at -78°C was added 2,6-di-tert-butyl-4-methylpyridine (632 mg, 3.08 mmol) followed by triflic anhydride (345  $\mu$ l, 2.05 mmol). After stirring 15 minutes at -78°C, the mixture was warmed to room temperature over 20 minutes, and then poured into a solution of saturated aqueous NaHCO<sub>3</sub> (20 ml) and extracted with ethyl acetate (50 ml). The organic layer was washed with saturated NaHCO<sub>3</sub> (3 x 20 ml), saturated aqueous NaCl (1 x 20 ml), and dried over magnesium sulfate. Concentration provided crude target compound, which was used in the next step without further purification.

D. Structure (13), Methyl 2,3,4-tri-O-benzyl-6-O-(N-trifluoroacetyl-5-aminopentyl)- $\beta$ -D-glucopyranoside

To a stirred suspension of sodium hydride (855 mg, 21.4 mmol, 60% oil dispersion) in 60 ml of dry THF at 0°C was added a solution of N-trifluoroacetyl-5-aminopentanol (1.7 g, 8.6 mmol) in 35 ml of dry THF. After stirring 10 minutes at 0°C, the suspension was warmed to room temperature, stirred for 1 hour, and cooled to 0°C. A solution of the above crude methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethylsulfonyl- $\beta$ -D-glucopyranoside (theoretically 1.71 mmol) in 57 ml of dry

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dichloromethane was added. The reaction mixture was stirred at 0°C for 30 minutes and then warmed to room temperature. After stirring 24 hours, the reaction was cooled to 0°C and quenched with 40 ml of saturated aqueous ammonium chloride.

5 The resulting solution was diluted with ethyl acetate (400 ml) and washed with H<sub>2</sub>O (1 x 150 ml), saturated aqueous NaCl (1 x 150 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 30% ethyl acetate in petroleum ether) provided the analog having structure (13), methyl

10 2,3,4-tri-O-benzyl-6-O-(N-trifluoroacetyl-5-aminopentyl)-β-D-glucopyranoside, (799 mg) as a white solid which was used without further purification.

**EXAMPLE 5**

Preparation of Analog Having Structure (8), Methyl 6-O-(5-aminopentyl)-2,3,4-tri-O-benzyl-β-D-glucopyranoside,

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To a stirred solution of methyl 2,3,4-tri-O-benzyl-6-O-(N-trifluoroacetyl-5-aminopentyl)-β-D-glucopyranoside (799 mg, theoretically 1.71 mmol, structure (13) from Example 4) in 10 ml of ethanol at room temperature was added a solution

20 of 5M NaOH (3 ml, 15 mmol). The solution was heated to reflux for 2 hours. The solvents were removed under reduced pressure. The reaction mixture was diluted with dichloromethane (70 ml) and washed with aqueous HCl (25 ml, 15 mmol). The water layer was re-extracted with

25 dichloromethane (3 x 50 ml), and the combined organic layers were washed with saturated aqueous NaCl (1 x 75 ml) and dried over magnesium sulfate. Concentration and crystallization from ethyl acetate/petroleum ether provided pure analog having structure (8), methyl 6-O-(5-aminopentyl)-2,3,4-tri-O-benzyl-

30 β-D-glucopyranoside, (675 mg, 72% from methyl 2,3,4-tri-O-benzyl-β-D-glucopyranoside) as a white solid; m.p. 95-95.5°C; R<sub>f</sub> 0.19 (6% methanol in dichloromethane); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35-7.24 (m, 15H), 4.32 (d, J = 7.5 Hz, 1H), 4.90 (d, J = 7.6 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.78 (d, J = 11.0 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.60 (d, J = 11.0 Hz, 1H), 4.32 (7.8, 1H), 3.66-3.59 (m, 3H), 3.56 (s, 3H), 3.48-

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3.36 (m, 3H), 2.94 (dd,  $J = 12.5, 2.1$  Hz, 1H), 2.68 (dd,  $J = 12.0, 6.8$  Hz, 1H), 2.64-2.53 (m, 2H), 1.71 (s, 2H), 1.59-1.53 (m, 2H), 1.51-1.45 (m, 2H), 1.42-1.36 (m, 2H),  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  138.55, 138.47, 138.17, 128.39, 128.33, 128.03, 127.95, 127.85, 127.77, 127.60, 127.57, 104.72, 84.56, 82.45, 79.74, 75.66, 75.02, 74.74, 74.16, 62.62, 57.20, 50.69, 49.72, 32.49, 29.65, 23.37; IR (thin film) 3280(m), 3095(w), 3065(w), 3035(w), 2935(s), 2915(s), 2860(s), 1496(w), 1454(m), 1404(w), 1393(w), 1358(m), 1214(m), 1115(s), 1072(s), 1037(m), 1027(m), 1009(m), 911(w), 826(w), 747(s), 696(s)  $\text{cm}^{-1}$ ; HRMS  $m/e$  calc'd for  $\text{C}_{33}\text{H}_{43}\text{O}_6\text{N}$  ( $M+H$ ): 550.3168, found 550.3179;  $[\alpha]_{\text{D}}^{20} +9.3^\circ$  ( $c=0.15$ , acetonitrile).

**EXAMPLE 6****Preparation of Analog Having Structure (12), 2-(1H-Indol-3-yl)ethyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside**

To a stirred solution of 2-(1-phenylsulfonyl-indol-3-yl)ethyl-2,3,4-tri-O-benzyl- $\beta$ -D-glucopyranoside (100 mg, 0.136 mmol, prepared in Example 1, step G) in 3 ml of ethanol at room temperature was added a solution of 5M NaOH (1 ml, 5 mmol). The reaction mixture was refluxed for 2h and the solvents were removed under reduced pressure. The resulting residue was diluted with dichloromethane (70 ml) and washed with aqueous HCl (24 ml, 5 mmol). The water layer was reextracted with dichloromethane (2 x 70 ml). The organic layers were combined and washed with saturated aqueous NaCl (1 x 50 ml) and dried over magnesium sulfate. Concentration and flash chromatography (silica, 25% ethyl acetate in petroleum ether) provided structure (12) (68 mg, 85%) as an oil:  $R_f$  0.42 (40% ethyl acetate in petroleum ether);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (s, 1H), 7.59 (d,  $J = 7.8$  Hz, 1H), 7.33-7.24 (m, 15H), 7.20-7.17 (m, 2H), 7.11 (t,  $J = 7.8$  Hz, 1H), 7.01 (d,  $J = 1.8$  Hz, 1H), 4.91 (d,  $J = 10.9$  Hz, 1H), 4.85 (d,  $J = 10.9$ , 1H), 4.80 (d,  $J = 10.9$  Hz, 1H), 4.79 (d,  $J = 11.0$  Hz, 1H), 4.64 (d,  $J = 11.0$  Hz, 1H), 4.63 (d,  $J = 11.0$  Hz, 1H), 4.49 (d,  $J = 7.8$  Hz, 1H), 4.22 (ddd,  $J = 9.4, 6.7, 6.7$  Hz, 1H), 3.90-3.82 (m, 2H), 3.72-3.67 (m, 1H), 3.65 (ap. t,

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$J = 9.1$  Hz, 1H), 3.56 (ap. t,  $J = 9.3$  Hz, 1H), 3.42 (ap. t,  $J = 8.1$  Hz, 1H), 3.35 (ddd,  $J = 9.5, 4.3, 2.8$  Hz, 1H), 3.11 (t,  $J = 7.0$  Hz, 2H), 1.87 (dd,  $J = 7.6, 5.9$  Hz, 1H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  138.52, 138.44, 137.98, 136.17, 128.46, 128.36, 128.29, 128.05, 128.00, 127.89, 127.86, 127.60, 127.57, 127.45, 122.09, 122.01, 119.34, 118.68, 112.60, 111.13, 103.69, 84.49, 82.34, 77.57, 75.64, 75.04, 75.01, 74.75, 70.25, 62.04, 25.86; IR (thin film) 3575(sh), 3435(m), 3085(sh), 3065(w), 3035(w), 2925(m), 2880(m), 1500(w), 1455(m), 1360(w), 1310(w), 1150(sh), 1085(s), 1030(s), 920(w), 810(w), 740(s), 700(s)  $\text{cm}^{-1}$ ; UV-Vis ( $c=2.89 \times 10^{-4}$ , acetonitrile)  $\lambda_{\text{max}}$  289.6 ( $\epsilon=3.56 \times 10^3$ ), 281.2 ( $\epsilon=4.24 \times 10^3$ ), 222.4 ( $\epsilon=1.01 \times 10^4$ ) nm; HR MS  $m/e$  calc'd for  $\text{C}_{37}\text{H}_{39}\text{O}_6\text{N}(\text{M} + \text{NH}_4)$ : 611.3121, found 611.3043;  $[\alpha]_D^{20} -2.5^\circ$  ( $c=1.37$ , acetonitrile).

**EXAMPLE 7**

Preparation of Analog Having Structure (10), 2-(1H-Indol-3-yl)ethyl-6-O-aminopentyl)-2,3-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside

20                   A.   Methyl 2,3,6-tri-O-benzoyl-4-(methylthio)thiocarbonyl- $\alpha$ -D-glucopyranoside

To a solution of the methyl 2,3,6-tri-O-benzoyl- $\alpha$ -D-glucopyranoside (5.00 g, 9.87 mmol) in 100 ml of dry THF at  $-78^\circ\text{C}$  was added carbon disulfide (0.45 ml, 7.48 mmol) followed by sodium bis(trimethylsilyl)amide (10.5 ml, 51.8 mmol). The solution was stirred at  $-78^\circ\text{C}$  for 20 minutes. Methyl iodide (2.10 ml, 33.7 mmol) was added, the solution was stirred for 5 minutes at  $-78^\circ\text{C}$  and then at room temperature for 45 minutes. The reaction was quenched by the addition of water (5 ml) and the mixture was extracted with ethyl acetate (2 X 100 ml). The organic layer was washed with a saturated solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield a pale yellow oil (5.70 g, 97%). The crude xanthate was used without purification in the next step. An analytical sample was purified by flash column chromatography using 20%



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ethyl acetate in petroleum ether to yield the target compound as white crystals.

**B. Methyl 2,3,6-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranoside**

5 To a solution of the crude methyl 2,3,6-tri O benzoyl-4-(methylthio)thiocarbonyl- $\alpha$ -D-glucopyranoside (5.70 g, 9.55 mmol) in 120 ml of dry toluene was added AIBN (50 mg). Tributyl tin hydride (6.68 ml, 24.8 mmol) was added and the reaction was heated to reflux for 4 hours. The toluene was removed under reduced pressure. Acetonitrile (200 ml) was added and the mixture extracted with petroleum ether (5 x 100 ml) to remove all tin salts. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure to yield a clear colorless oil which solidified on standing. 10 Purification by flash column chromatography using 20% ethyl acetate in petroleum ether as the eluant gave the target compound as a white solid.

**C. 1-O-Acetyl-2,3,6-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranose**

20 To a solution of methyl 2,3,6-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranoside (0.50 g, 1.1 mmol) in acetic anhydride (3.0 ml, 32 mmol) at 0°C was added boron trifluoride etherate (0.1 ml). The solution was stirred at room temperature for 4 hours, diluted with ethyl acetate and poured in an ice-cold solution of saturated sodium bicarbonate. Extraction with 25 ethyl acetate (2 X 100 ml) was followed by washing with a saturated solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield the product as a colorless oil which 30 crystallized upon standing to give the target compound as white needles (0.45 g, 85%).

**D. 1-Bromo-2,3,6-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranose**

To a stirred solution of 1-O-acetyl-2,3,6-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranose (0.137 g, 0.29 mmol) in 3.0 ml of dry dichloromethane at 0°C was added 30% hydrogen bromide in acetic acid (0.07 ml, 0.33 mmol). The solution was

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stirred under argon at room temperature for 4 hours, diluted with ethyl acetate (100 ml) and extracted with a saturated solution of sodium bicarbonate. The organic layer was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield the target compound as a colorless oil which solidified upon standing. Crystallization from ether and petroleum ether gave the target compound as white crystals (0.15 g, 100%).

10           E.    2-(1-Phenylsulfonyl)-indol-3-yl-ethyl-2,3,6-tri-O-benzoyl-4-deoxy- $\beta$ -D-glucopyranoside

To a mixture of activated powdered 4Å molecular sieves (0.83 g), the protected tryptophol prepared in Example 1, step B (0.37 g, 1.23 mmol) and silver (I) oxide (0.83 g, 3.58 mmol) in a flask wrapped with aluminum foil was added a solution of 1-bromo-2,3,6,-tri-O-benzoyl-4-deoxy- $\alpha$ -D-glucopyranose (0.40 g, 0.814 mmol) in 16.7 ml of 40% hexane in benzene. The mixture was stirred under argon for two days, filtered through celite, washed with ethyl acetate and the solvent was removed to yield a colorless oil. Purification by flash column chromatography using 50% ether in petroleum ether gave the target compound as a colorless solid (0.50 g, 81%).

25           F.    2-(1-Phenylsulfonyl)-indol-3-yl-ethyl-4-deoxy- $\beta$ -D-glucopyranoside

To a solution of 2-(1-phenylsulfonyl)-indol-3-yl-ethyl-2,3,6-tri-O-benzoyl-4-deoxy- $\beta$ -D-glucopyranoside (120 mg, 0.158 mmol) in 20 ml of methanol was added sodium methoxide (0.027 g, 0.507 mmol). The solution was stirred under argon overnight. Amberlyst H+ resin was added and the reaction stirred until neutral to wet pH paper. The resin was removed by filtration and washed with methanol. The filtrate was concentrated under reduced pressure to yield a tan solid. Purification by flash column chromatography using 10% methanol in dichloromethane gave the target compound as a white solid (65 mg, 91%).

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G. 2-(1-Phenylsulfonyl)-indol-3-yl-ethyl-6-O-  
tert-butyldiphenylsilyl-4-deoxy- $\beta$ -D-  
glucopyranoside

To a solution of 2-(1-phenylsulfonyl)-indol-3-yl-  
5 ethyl-4-deoxy- $\beta$ -D-glucopyranoside (0.24 g, 0.536 mmol) in 6  
ml of dry DMF was added imidazole (73 mg, 1.07 mmol) followed  
by tert-butyldiphenylsilyl chloride (0.17 ml, 0.643 mmol).  
The solution was heated under argon in an oil bath at 70°C for  
48 hours. The reaction was quenched by addition of methanol  
10 (5 ml). The solvents were removed under reduced pressure.  
The residue was extracted with ethyl acetate (2 x 200 ml),  
washed with a saturated solution of sodium chloride and dried  
over anhydrous sodium sulfate. Removal of the solvent under  
reduced pressure gave a pale yellow oil. Purification by  
15 flash column chromatography using 3% methanol in  
dichloromethane gave the target compound as a colorless oil  
(0.36 g, 97%).

H. 2-(1-Phenylsulfonyl)-indol-3-yl-ethyl-2,3,-di-  
O-benzyl-6-O-tert-butyldiphenylsilyl-4-deoxy-  
20  $\beta$ -D-glucopyranoside

To a stirred suspension of sodium hydride (73.0 mg,  
3.04 mmol, 60% oil dispersion) in 2.7 ml of dry THF at 0°C was  
added a solution of 2-(1-phenylsulfonyl)-indol-3-yl-ethyl-6-O-  
tert-butyldiphenylsilyl-4-deoxy- $\beta$ -D-glucopyranoside (0.50 g,  
25 0.729 mmol) in dry THF (6.8 ml). The reaction mixture was  
stirred at room temperature for 30 minutes. The mixture was  
cooled to 0°C and benzyl bromide (0.26 ml, 2.18 mmol) was  
added dropwise. After stirring at room temperature for 3  
days, the reaction was quenched by addition of ammonium  
30 chloride (10 ml) followed by extraction with ether (2 X 100  
ml). The organic layer was washed with a saturated solution  
of sodium chloride, dried over anhydrous sodium sulfate and  
evaporated under reduced pressure to yield a pale yellow oil.  
Purification by flash column chromatography using 33% ether  
35 in petroleum ether afforded the target compound as a colorless  
oil (0.73 g, 76%).

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I. 2-(1-Phenylsulfonyl)-indol-3-yl-ethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside

To a solution of the 2-(1-phenylsulfonyl)-indol-3-yl-ethyl-2,3,-di-O-benzyl-6-O-tert-butyl-diphenylsilyl-4-deoxy- $\beta$ -D-glucopyranoside (0.37 g, 0.427 mmol) in 10.5 ml of dry THF was added tetrabutylammonium fluoride (1.33 ml, 1M in THF, 1.33 mmol). The solution was stirred under argon for 3 hours, diluted with ethyl acetate (100 ml) and washed with water (100 ml). The organic layer was washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure yielded a pale yellow oil. Purification by flash column chromatography using 33% petroleum ether in ethyl acetate yielded the target compound as a colorless oil (0.43 g, 85%).

J. 2-indol-3-yl-ethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside

To a solution of the 2-(1-phenylsulfonyl)-indol-3-yl-ethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside (140 mg, 0.223 mmol) in 6.0 ml of ethanol was added 5 M NaOH (2 ml) and the solution heated to reflux for 2 hours. The solvents were removed under reduced pressure and the residue taken up in water (100 ml) and extracted with ethyl acetate (3 X 100 ml). The organic phase was washed with a saturated solution of sodium chloride, dried with anhydrous sodium sulfate and concentrated to yield a colorless oil. Purification by flash column chromatography using 3% methanol in dichloromethane yielded the target compound as a colorless oil (100 mg, 92%).

K. 5-Phthalimido-1-pentanol

To a solution of 5-amino-1-pentanol (5.00 g, 48.5 mmol) in benzene (150 ml) was added N-carboethoxyphthalimide (11.0 g, 50.2 mmol) and the solution was stirred at room temperature for 5 h). The solvents were removed under reduced pressure to yield a yellow oil. Purification by flash column chromatography using 25% ethyl acetate in petroleum ether yielded the target compound as a clear colorless oil (9.6 mg, 84%).

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**L. 5-Phthalimido-1-O-trifluoromethane-sulfonylpentanol**

To a solution of 5-phthalimido-1-pentanol (39.1 mg, 0.168 mmol) in dry dichloromethane (1.5 ml) was added 2,6-di-  
5 tert-butyl-4-methylpyridine (34.5 mg, 0.168 mmol) followed by triflic anhydride (28.3  $\mu$ l, 0.168 mmol). The solution was stirred at room temperature for 10 minutes. The reaction was poured into water (25 ml) and extracted with dichloromethane (2 x 50 ml). The organic layer was washed with a saturated  
10 sodium chloride solution and dried with anhydrous sodium sulfate. The solvents were removed under reduced pressure to yield a pale yellow solid which was used immediately without further purification.

**M. 2-(1-Phenylsulfonyl-3-yl)ethyl-2,3-di-O-benzyl-4-deoxy-6-O(phthalimidopentyl)- $\beta$ -D-glucopyranoside**

To a solution of 5-phthalimido-1-O-trifluoromethanesulfonylpentanol (theoretically 0.168 mmol) in dry dichloromethane (1.5 ml) was added 2,6-di-tert-butyl-4-  
20 methylpyridine (34.5 mg, 0.168 mmol). The solution was cooled to 0°C and to it was added a solution of 2-indol-3-yl-ethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside (18.4 mg, 0.029 mmol, from step J, above) in dry dichloromethane (1.5 ml). The solution was stirred for 30 minutes at 0°C and then sodium  
25 hydride (7.0 mg, 0.29 mmol, 60% dispersion in oil) was added. Stirring was continued at 0°C for 1 hour and then at room temperature for 24 hours. The reaction was poured into water (50 ml) and extracted with dichloromethane (2 x 100 ml). The organic layers were combined and washed with a saturated  
30 sodium chloride solution followed by drying with anhydrous sodium sulfate. The solvents were removed under reduced pressure to yield a pale yellow oil. Purification by flash column chromatography using 20% ethyl acetate in petroleum ether yielded the target compound as a clear colorless oil  
35 (19.4 mg, 80%).

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N. Structure (10), 2-(1H-Indol-3-yl)ethyl-6-O-aminopentyl)-2,3-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside

To a solution of 2-(1-phenylsulfonyl-3-yl)ethyl-2,3-di-O-benzyl-4-deoxy-6-O(phthalimidopentyl)- $\beta$ -D-glucopyranoside (150 mg, 0.178 mmol) in methanol (8 ml) was added sodium methoxide (40 mg, 0.740 mmol). The solution was heated to reflux for 24 hours. The reaction was poured into water (100 ml) and extracted with dichloromethane (2 x 100 ml). The organic layers were combined and washed with a saturated solution of sodium chloride and dried with anhydrous sodium sulfate. Concentration of the solvents under reduced pressure yielded a pale yellow oil. Purification by flash column chromatography using 10% methanol in dichloromethane yielded structure (10) as a colorless oil (72.0 mg, 71%)  $R_f$  0.32 (10% methanol in dichloromethane);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (brm, 1H), 7.48 (d,  $J$  = 7.8 Hz, 1H), 7.36-6.93 (m, 15H), 4.62-4.49 (m, 4H), 4.32 (d,  $J$  = 7.7 Hz, 1H), 4.11 (dt,  $J$  = 9.4, 6.7 Hz, 1H), 3.78 (dt, 9.2, 7.4 Hz, 1H), 3.52 (m, 4H), 3.26 (m, 2H), 3.22 (t,  $J$  = 7.2 Hz, 1H), 3.13 (t,  $J$  = 7.8 Hz, 1H), 3.00 (t,  $J$  = 7.0 Hz, 2H), 2.00 (ddd,  $J$  = 6.7, 5.2, 1.4 Hz, 1H), 1.29 (m, 9H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  140.11, 138.10, 130.75, 130.59, 129.31, 128.92, 128.84, 128.57, 128.44, 123.79, 122.24, 119.40, 112.82, 112.31, 105.01, 84.13, 79.55, 75.76, 74.12, 73.12, 72.53, 72.18, 71.29, 41.05, 34.54, 30.38, 29.90, 27.07, 24.72, IR ( $\text{CHCl}_3$ ) 3350, 3060, 2930, 2860, 1630, 1520, 1450, 1400, 1270, 1100, 740, 700; UV ( $c=1.57 \times 10^{-4}\text{M}$ , acetonitrile)  $\lambda_{\text{max}}$  280.0 ( $\epsilon=1.41 \times 10^3$ ), 224.8 ( $\epsilon=1.66 \times 10^3$ ) nm; HRMS  $m/e$  calc'd for  $\text{C}_{35}\text{H}_{45}\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}$ ): 573.3328, found 573.3301;  $[\alpha]_{\text{D}^{20}} + 3.89^\circ$  ( $c=1.8$ , acetonitrile).

EXAMPLE 8

Preparation of Analog Having Structure (11), 2-Indol-3-ylethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside

To a solution of 2-(1-phenylsulfonyl)-indol-3-ylethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -D-glucopyranoside (140 mg, 0.223 mmol, from Example 7, step I, above) in 6.0 ml of

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ethanol was added 5M NaOH (2 ml) and the solution heated to reflux for 2 hours. The solvents were removed under reduced pressure and the residue taken up in water (100 ml) and extracted with ethyl acetate (3 X 100 ml). The organic phase  
5 was washed with a saturated solution of sodium chloride, dried with anhydrous sodium sulfate and concentrated to yield a colorless oil. Purification by flash column chromatography using 3% methanol in dichloromethane yielded the analog having structure (11) (2-indol-3-yl-ethyl-2,3,-di-O-benzyl-4-deoxy- $\beta$ -  
10 D-glucopyranoside) as a colorless oil (100 mg, 92%).  $R_f$  0.59 (10% methanol in dichloromethane);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (br s, 1H), 7.59 (d,  $J$  = 7.8 Hz, 1H), 7.31-6.99 (m, 14H), 4.78-4.66 (m, 4H), 4.41 (d,  $J$  = 7.7 Hz, 1H), 4.22 (dt,  $J$  = 9.4, 7.4 Hz, 1H), 3.61-3.56 (m, 3H), 3.49-3.45 (m, 1H), 3.32  
15 (t,  $J$  = 7.9 Hz, 1H), 3.11 (t,  $J$  = 6.9 Hz, 2H), 2.03 (br s, 1H), 1.95 (ddd,  $J$  = 12.8, 5.3, 1.8 Hz, 1H), 1.49 (q,  $J$  = 11.7 Hz, 1H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  138.72, 138.48, 136.12, 128.33, 128.20, 127.97, 127.60, 127.56, 127.46, 122.15, 121.92, 119.27, 118.66, 112.57, 111.10, 103.87, 82.81, 78.10,  
20 74.86, 72.23, 72.13, 70.18, 65.17, 32.69, 25.84; UV-Vis ( $c$  =  $1.85 \times 10^{-4}$ , acetonitrile)  $\lambda_{\text{max}}$  281.2 ( $\xi$  = 614.13), 222.0 ( $\xi$  = 864.86) nm; HRMS  $m/e$  calculated for  $\text{C}_{30}\text{H}_{34}\text{NO}_5$  ( $M+H$ ): 488.2436, found 488.2483;  $[\alpha]_D^{20}$  +5.55° ( $c$  = 1.8, acetonitrile).

**EXAMPLE 9**

25 The affinity of a variety of compounds for the substance P receptor was determined employing the following procedure.

**A. Receptor Expression in COS**

To express the cloned human neurokinin-1 receptor  
30 (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (Invitrogen) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from Bluescript SK+) into the Sac II site. Transfection of 20  $\mu\text{g}$  of the plasmid DNA into 10  
35 million COS cells was achieved by electroporation in 800  $\mu\text{l}$  of transfection buffer (135 mM NaCl, 1.2 mM  $\text{CaCl}_2$ , 1.2 mM

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MgCl<sub>2</sub>, 2.4 mM K<sub>2</sub>HPO<sub>4</sub>, 0.6 mM KH<sub>2</sub>PO<sub>4</sub>, 10 nM glucose, 10 mM HEPES pH 7.4) at 260 V and 950  $\mu$ F using the IBI Genezapper (IBI, New Haven, CT). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100 U/ml penicillin-streptomycin, and 90% DMEM media (Gibco, Grand Island, NY) in 5% CO<sub>2</sub> at 37°C for three days before the binding assay.

**B. Assay Protocol using COS**

The binding assay of human NK1R expressed in COS cells is based on the use of <sup>125</sup>I-substance P (<sup>125</sup>I-SP, from DuPont, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS were dissociated by the non-enzymatic solution (Specialty Media, Lavallette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM MnCl<sub>2</sub>, 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200  $\mu$ l of the cell suspension would give rise to about 10,000 cpm of specific <sup>125</sup>I-SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200  $\mu$ l of cells were added to a tube containing 20  $\mu$ l of 1.5 to 2.5 nM of <sup>125</sup>I-SP and 20  $\mu$ l of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (Brandel, Gaithersburg, MD) which was pre-wetted with 0.1 polyethylenimine. The filter was washed with 3 ml of wash buffer (50 Tris pH 7.5, 5 mM MnCl<sub>2</sub>, 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

A variety of compounds were tested according to the COS cell procedure. The concentration of compound required to inhibit the binding of substance P to the human neurokinin-1 receptor by 50% was measured, and the following data were obtained:



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	<u>Compound</u>	<u>IC<sub>50</sub></u>
	1	120 nM
	2	180 nM
	7	56 nM
5	8	840 nM
	9	400 nM
	11	400 nM
	13	1000 nM

**EXAMPLE 10**

10           The affinity of a variety of compounds for the SRIF  
 receptor was determined by studying the displacement of <sup>125</sup>I-  
 CGP-23996 from AtT-20 cells using a method generally in  
 accordance with that disclosed by Raynor and Reisine, *Journal*  
*of Pharmacology and Experimental Therapeutics*, 1989, 251;2,  
 15 510. The following data were obtained:

	<u>Compound</u>	<u>IC<sub>50</sub></u>
	1	9500 nM
	2	1300 nM
	8	40000 nM
20	13	does not bind
	SRIF	9.3 nM
	MK 678	60 nM
	L-363,301	18.7 nM

**EXAMPLE 11**

25           The affinity of a 2-(1-phenylsulfonyl-indol-  
 3yl)ethyl-6-O-(5-aminopentyl)-2,3,4-tri-O-benzyl-β-D-  
 glucopyranoside, structure (1) and methyl 6-O-(5-aminopentyl)-  
 2,3,4-tri-O-benzyl-β-D-glucopyranoside, structure (8) for a  
 variety of G-protein-linked receptors was determined by  
 30 studying the displacement of a variety of radioligands from  
 AtT-20 and brain cells using a method generally in accordance  
 with that disclosed by Reisine, et al., *Brain Research*, 1979,  
 177, 241. The following data was obtained (<sup>125</sup>I-CYP = <sup>125</sup>I-  
 cyanopindolol; <sup>3</sup>H-QNB = quinuclidinyl benzilate):

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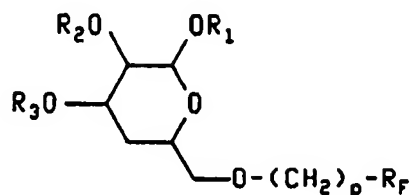
<u>Receptor</u>	<u>Radioligand (conc.)</u>	<u>Compound</u>	<u>Binding Inhibition</u>	<u>Tissue</u>
5 $\beta$ -Adrenergic	$^{125}\text{I}$ -CYP (0.1 nM)	1	70%	AtT-20
		1	45	Brain
		8	0	AtT-20
Opiate Receptor	$^3\text{H}$ -naloxone (0.5 nM)	1	55	Brain
Dopamine Receptor	$^3\text{H}$ -spiperone (0.1 nM)	1	82	Brain
10 Muscarinic cholinergic	$^3\text{H}$ -QNB (0.1 nM)	1	20	AtT-20
		1	83	Brain

As can be seen from Examples 9-11, the peptide  
analogs of the present invention are selectively bound by  
certain receptors. For example, structure (1) exhibits  
approximately 14-fold greater selectivity than structure (8)  
for the substance P receptor, while structure (8) is bound by  
the substance P and SRIF receptors but is not bound by the  $\beta$ -  
adrenergic receptor.

Those skilled in the art will appreciate that  
numerous changes and modifications may be made to the  
preferred embodiments of the invention and that such changes  
and modifications may be made without departing from the  
spirit of the invention. It is therefore intended that the  
appended claims cover all such equivalent variations as fall  
within the true spirit and scope of the invention.

## WHAT IS CLAIMED IS:

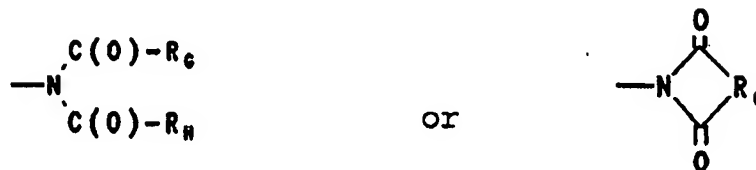
1. A process for preparing a protected amine compound having structure:



wherein:

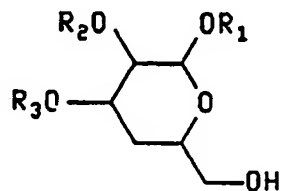
$R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups and

$R_F$  has structure:



where  $R_6$  and  $R_8$  are, independently, alkyl or alkenyl having from one to about 10 carbon atoms, and  $p$  is an integer from 0 to about 10; comprising the steps of:

providing a first compound having structure:



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contacting said first compound with a second compound having structure:



where L is a leaving group, said contacting being effected in the presence of a base under conditions that do not remove said hydroxyl protecting groups  $R_1$ ,  $R_2$ , and  $R_3$ .

2. The process of claim 1 wherein:

$R_1$  is 2-(1-phenylsulfonyl)-indol-3-yl-ethyl and  $R_2$  and  $R_3$  are benzyl;

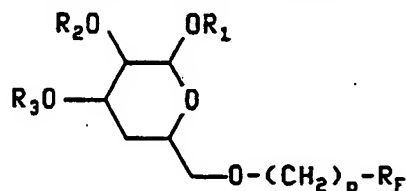
$R_F$  is phthalimido;

p is about 5; and

L is O-trifluoromethanesulfonyl.

3. The process of claim 1 wherein said base is 2,6-di-tert-butyl-4-methylpyridine or 2,4,6-trimethylpyridine.

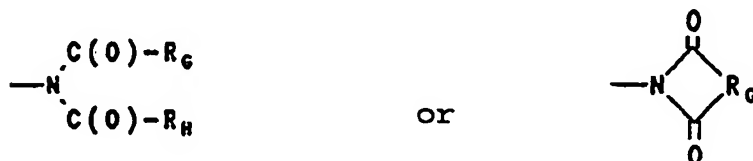
4. A protected amine compound having structure:



wherein:

$R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups; and

$R_F$  has structure:



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where  $R_G$  and  $R_H$  are, independently, alkyl or alkenyl having from one to about 10 carbon atoms, and  $p$  is an integer from 0 to about 10.

5. The compound of claim 4 wherein  $R_1$ ,  $R_2$ , and  $R_3$  are, independently, 2-(1-phenylsulfonyl)-indol-3-yl-ethyl or benzyl.

6. The compound of claim 4 wherein  $R_1$  is 2-(1-phenylsulfonyl)-indol-3-yl-ethyl.

7. The compound of claim 4 wherein  $R_2$  and  $R_3$  are benzyl.

8. The compound of claim 4 wherein  $R_1$  is 2-(1-phenylsulfonyl)-indol-3-yl-ethyl and  $R_2$  and  $R_3$  are benzyl.

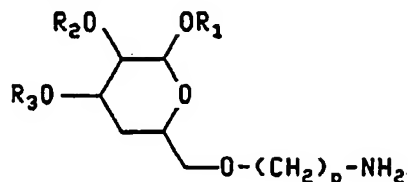
9. The compound of claim 4 wherein  $p$  is about 5.

10. The compound of claim 4 wherein  $R_G$  and  $R_H$  are alkyl having 1 to about 3 carbon atoms.

11. The compound of claim 4 wherein  $R_F$  is phthalimido.

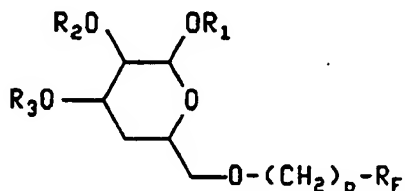
- 60 -

12. A process for preparing a primary amine compound having structure:



wherein  $R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups and  $p$  is an integer from 1 to about 10, comprising the steps of:

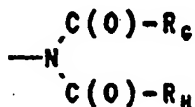
providing a first compound having structure:



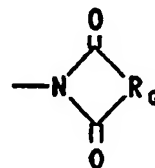
wherein:

$R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups; and

$R_f$  has structure:



or



where  $R_g$  and  $R_h$  are, independently, alkyl or alkenyl having from one to about 10 carbon atoms; and contacting said first compound with a base that does not remove said hydroxyl protecting groups  $R_1$ ,  $R_2$ , or  $R_3$ .

13. The process of claim 12 wherein:

$R_1$  is 2-(1-H-indol-3-yl)ethyl and  $R_2$  and  $R_3$  are benzyl;

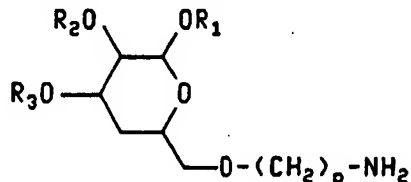
$R_f$  is phthalimido;

$p$  is about 5,

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14. The process of claim 12 wherein said base is sodium methoxide or sodium ethoxide.

15. A primary amine compound having structure:



wherein:

$R_1$ ,  $R_2$ , and  $R_3$  are the same or different and are hydroxyl protecting groups; and

$p$  is an integer from 1 to about 10.

16. The compound of claim 15 wherein  $R_1$ ,  $R_2$ , and  $R_3$  are, independently, 2-(1-H-indol-3-yl)ethyl or benzyl

17. The compound of claim 15 wherein  $R_1$  is 2-(1-H-indol-3-yl)ethyl.

18. The compound of claim 15 wherein  $R_2$  and  $R_3$  are benzyl.

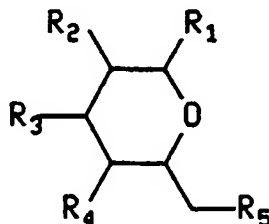
19. The compound of claim 15 wherein  $R_1$  is 2-(1-H-indol-3-yl)ethyl and  $R_2$  and  $R_3$  are benzyl.

20. The compound of claim 15 wherein  $p$  is about 5.

## AMENDED CLAIMS

[received by the International Bureau on 12 July 1993 (12.07.93);  
new claims 21-33 added; other claims unchanged (7 pages)]

21. A compound having the structure:



wherein:

$R_1$  is  $-O(CH_2)_nR_A$ ,  $-OC(O)(CH_2)_nR_A$ ,  $-(CH_2)_nR_A$ , or  $-C(O)(CH_2)_nR_A$  where  $R_A$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, aryl having from about 6 to about 14 carbon atoms, or heteroaryl having about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, and  $n$  is an integer from 0 to about 12;

at least one of  $R_2$ ,  $R_3$ , and  $R_4$ , independently, is

$-O(CH_2)_yH$ ,  $-O(CH_2)_mR_B$ ,  $-OC(O)(CH_2)_mR_B$ ,  $-(CH_2)_mR_B$  or  $-C(O)(CH_2)_mR_B$  where  $R_B$  is aryl having from about 6 to about 14 carbon atoms,  $y$  is an integer from 1 to about 5, and  $m$  is an integer from 0 to about 5; and

$R_5$  is  $-O(CH_2)_pNHR_C$ ,  $-OC(O)(CH_2)_pNHR_C$ ,  $-O(CH_2)_pR_D$ ,  $-OC(O)(CH_2)_pR_D$ ,  $-(CH_2)_pNHR_C$ ,  $-C(O)(CH_2)_pNHR_C$ ,  $-(CH_2)_pR_D$  or  $-C(O)(CH_2)_pR_D$ , where:

$p$  is an integer from 0 to about 10;

$R_C$  is  $-R_E$  or  $-C(O)R_E$ ;

$R_D$  is  $-H$ ,  $-OR_E$ , or  $-C(O)R_E$ ;

$R_E$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl



or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms,  
aryl having from about 6 to about 14 carbon atoms,  
or heteroaryl having from about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms;  
or a pharmaceutically acceptable salt thereof, provided that:  
at least one of  $R_1$ - $R_5$  includes an aryl or heteroaryl moiety having from about 6 to about 14 carbon atoms; and  
 $R_1$  is not  $-O(CH_2)_2(3\text{-indole})$  where  $R_2$  and  $R_4$  are  $-O$ -benzyl,  $R_3$  is  $-O$ -benzyl or  $-H$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

22. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O$ -benzyl; and  $R_5$  is  $-O(CH_2)_5NH_2$ .

23. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$  and  $R_4$  are  $-O$ -benzyl;  $R_3$  is  $-OH$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

24. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O$ -benzyl; and  $R_5$  is  $-O(CH_2)_5NHC(O)CH_3$ .

25. The compound of claim 21 wherein  $R_1$  is  $-OCH_3$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O$ -benzyl; and  $R_5$  is  $-O(CH_2)_5NH_2$ .

26. The compound of claim 21 wherein  $R_1$  is  $-OCH_3$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O$ -benzyl; and  $R_5$  is  $-O(CH_2)_5NHC(O)CH_3$ .

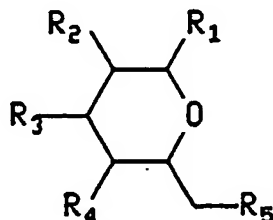
27. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$  and  $R_3$  are  $-O$ -benzyl;  $R_4$  is  $-OH$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

28. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$  and  $R_3$  are  $-O$ -benzyl;  $R_4$  is  $-OH$ , and  $R_5$  is  $-O(CH_2)_5OH$ .

29. The compound of claim 21 wherein  $R_1$  is  $-O(CH_2)_2(3\text{-indole})$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O\text{-benzyl}$ ; and  $R_5$  is  $-O(CH_2)OH$ .

30. The compound of claim 21 wherein  $R_1$  is  $-OCH_3$ ;  $R_2$ ,  $R_3$ , and  $R_4$  are  $-O\text{-benzyl}$ ; and  $R_5$  is  $-O(CH_2)OH$ .

31. A method for modulating the activity of at least one mammalian G-protein-linked receptor, comprising contacting said receptor with an effective amount of a compound having the structure:



wherein:

$R_1$  is  $-O(CH_2)_nR_A$ ,  $-OC(O)(CH_2)_nR_A$ ,  $-(CH_2)_nR_A$ , or  $-C(O)(CH_2)_nR_A$  where  $R_A$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms; aryl having from about 6 to about 14 carbon atoms, or heteroaryl having about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, and  $n$  is an integer from 0 to about 12;

at least one of  $R_2$ ,  $R_3$ , and  $R_4$ , independently, is

$-O(CH_2)_yH$ ,  $-O(CH_2)_mR_B$ ,  $-OC(O)(CH_2)_mR_B$ ,  $-(CH_2)_mR_B$  or  $-C(O)(CH_2)_mR_B$  where  $R_B$  is aryl having from about 6 to about 14 carbon atoms,  $y$  is an integer from 1 to about 5, and  $m$  is an integer from 0 to about 5; and

$R_5$  is  $-O(CH_2)_pNHR_C$ ,  $-OC(O)(CH_2)_pNHR_C$ ,  $-O(CH_2)_pR_D$ ,  $-OC(O)(CH_2)_pR_D$ ,  $-(CH_2)_pNHR_C$ ,  $-C(O)(CH_2)_pNHR_C$ ,  $-(CH_2)_pR_D$  or  $-C(O)(CH_2)_pR_D$ , where:

$p$  is an integer from 0 to about 10;

$R_C$  is  $-R_E$  or  $-C(O)R_E$ ;

$R_D$  is  $-H$ ,  $-OR_E$ , or  $-C(O)R_E$ ;

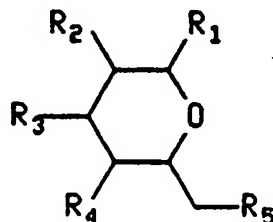
$R_E$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, aryl having from about 6 to about 14 carbon atoms, or heteroaryl having from about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms;

or a pharmaceutically acceptable salt thereof, provided that:

at least one of  $R_1$ - $R_5$  includes an aryl or heteroaryl moiety having from about 6 to about 14 carbon atoms; and

$R_1$  is not  $-O(CH_2)_2(3\text{-indole})$  where  $R_2$  and  $R_4$  are  $-O$ -benzyl,  $R_3$  is  $-O$ -benzyl or  $-H$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

32. A method for modulating the activity of at least one mammalian Substance P receptor, comprising contacting said receptor with an effective amount of a compound having the structure:



wherein:

$R_1$  is  $-O(CH_2)_nR_A$ ,  $-OC(O)(CH_2)_nR_A$ ,  $-(CH_2)_nR_A$ , or  $-C(O)(CH_2)_nR_A$  where  $R_A$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to

about 14 carbon atoms and 1 to about 4 nitrogen atoms, aryl having from about 6 to about 14 carbon atoms, or heteroaryl having about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, and  $n$  is an integer from 0 to about 12;

at least one of  $R_2$ ,  $R_3$ , and  $R_4$ , independently, is

$-O(CH_2)_yH$ ,  $-O(CH_2)_mR_B$ ,  $-OC(O)(CH_2)_mR_B$ ,  $-(CH_2)_mR_B$  or  $-C(O)(CH_2)_mR_B$  where  $R_B$  is aryl having from about 6 to about 14 carbon atoms,  $y$  is an integer from 1 to about 5, and  $m$  is an integer from 0 to about 5; and

$R_5$  is  $-O(CH_2)_pNHR_C$ ,  $-OC(O)(CH_2)_pNHR_C$ ,  $-O(CH_2)_pR_D$ ,  $-OC(O)(CH_2)_pR_D$ ,  $-(CH_2)_pNHR_C$ ,  $-C(O)(CH_2)_pNHR_C$ ,  $-(CH_2)_pR_D$  or  $-C(O)(CH_2)_pR_D$ , where:

$p$  is an integer from 0 to about 10;

$R_C$  is  $-R_E$  or  $-C(O)R_E$ ;

$R_D$  is  $-H$ ,  $-OR_E$ , or  $-C(O)R_E$ ;

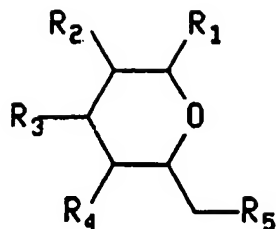
$R_E$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, aryl having from about 6 to about 14 carbon atoms, or heteroaryl having from about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms;

or a pharmaceutically acceptable salt thereof, provided that:

at least one of  $R_1$ - $R_5$  includes an aryl or heteroaryl moiety having from about 6 to about 14 carbon atoms; and

$R_1$  is not  $-O(CH_2)_2(3\text{-indole})$  where  $R_2$  and  $R_4$  are  $-O$ -benzyl,  $R_3$  is  $-O$ -benzyl or  $-H$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

33. A method for mimicking or inhibiting the chemical activity of a peptide, comprising providing in place of the peptide at least one chemical compound having the structure:



wherein:

$R_1$  is  $-O(CH_2)_nR_A$ ,  $-OC(O)(CH_2)_nR_A$ ,  $-(CH_2)_nR_A$ , or  $-C(O)(CH_2)_nR_A$  where  $R_A$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, aryl having from about 6 to about 14 carbon atoms, or heteroaryl having about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms, and  $n$  is an integer from 0 to about 12;

at least one of  $R_2$ ,  $R_3$ , and  $R_4$ , independently, is

$-O(CH_2)_yH$ ,  $-O(CH_2)_mR_B$ ,  $-OC(O)(CH_2)_mR_B$ ,  $-(CH_2)_mR_B$  or  $-C(O)(CH_2)_mR_B$  where  $R_B$  is aryl having from about 6 to about 14 carbon atoms,  $y$  is an integer from 1 to about 5, and  $m$  is an integer from 0 to about 5; and

$R_5$  is  $-O(CH_2)_pNHR_C$ ,  $-OC(O)(CH_2)_pNHR_C$ ,  $-O(CH_2)_pR_D$ ,  $-OC(O)(CH_2)_pR_D$ ,  $-(CH_2)_pNHR_C$ ,  $-C(O)(CH_2)_pNHR_C$ ,  $-(CH_2)_pR_D$  or  $-C(O)(CH_2)_pR_D$ , where:

$p$  is an integer from 0 to about 10;

$R_C$  is  $-R_E$  or  $-C(O)R_E$ ;

$R_D$  is  $-H$ ,  $-OR_E$ , or  $-C(O)R_E$ ;

$R_E$  is  $-H$ , alkyl or alkenyl having from about 1 to about 14 carbon atoms, heteroalkyl

or heteroalkenyl having about 1 to about 14 carbon atoms and 1 to about 4 n atoms, - aryl having from about 6 to about 14 carbon atoms, or heteroaryl having from about 6 to about 14 carbon atoms and 1 to about 4 nitrogen atoms;

or a pharmaceutically acceptable salt thereof, provided that:

at least one of  $R_1$ - $R_5$  includes an aryl or heteroaryl moiety having from about 6 to about 14 carbon atoms; and

$R_1$  is not  $-O(CH_2)_2(3\text{-indole})$  where  $R_2$  and  $R_4$  are  $-O$ -benzyl,  $R_3$  is  $-O$ -benzyl or  $-H$ , and  $R_5$  is  $-O(CH_2)_5NH_2$ .

## STATEMENT UNDER ARTICLE 19

In response to the International Search Report mailed May 12, 1993, in connection with the above-identified patent application, Applicants wish to add claims 21-33. These claims find support in the specification at, for example, page 15, lines 1-27 and page 21, line 31 - page 25, line 28.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01201

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :C07H 1/00, 15/00, 17/00

US CL :536/17.2, 17.4, 17.9, 18.5, 18.6, 18.7, 55.3

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/17.2, 17.4, 17.9, 18.5, 18.6, 18.7, 55.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,663,444 (Egan) 05 May 1987, col. 2, lines 53-68 and col. 3, lines 1-10.	1-3 and 12-14
X	Chemical Abstracts, vol. 114, no. 11, issued 1991, Nicolaou et al, pages 825-826, abstract no. 102793a, "Design and synthesis of a peptidomimetic employing beta-D-glucose for scaffolding", Pept.; Chem., Struct. Biol., Proc. Am. Pept. Symp., 11th 1989 (pub. 1990), pages 881-884.	4-11 and 15-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

28 April 1993

Date of mailing of the international search report

12 MAY 1993

Name and mailing address of the ISA/US  
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